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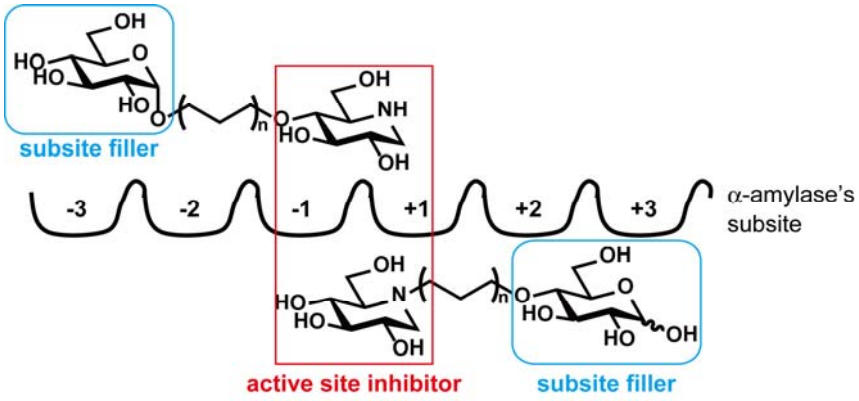
Graphical abstract



Synthesis and alpha-amylase inhibitory activity of glucose-deoxynojirimycin conjugates

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Abstract

α-amylase inhibitor has attracted attentions from its prospective effect against diabetes mellitus. Although numerous studies have focused on exploring natural small molecule inhibitor, acarbose is the only compound found to have sufficient strength of inhibition and character to be used as chemical treatment. We have synthesized a conjugate of 1-deoxynojirimycin, a strong glucosidase inhibitor, and glucose prospecting to raise an inhibitory activity against α-amylase. The synthetic conjugate showed increased inhibition against α-amylase then 1-deoxynojirimycin alone, giving us opportunity of developing efficient α-amylase inhibitor by modifying the existing glucosidase inhibitors.

Keywords

α-amylase inhibitor, 1-deoxynojirimycin, porcine pancreatic amylase, diabetes mellitus

1. Introduction

Glucosidases are contributing to variety of crucial steps in our body. One of those steps is the digestion of polysaccharides relating to our energy intake. Several different glucosidases participate in this event including salivary/pancreatic α-amylase and intestinal α-glucosidases (maltase-glucoamylase complex and sucrase-isomaltase complex). These enzymes hydrolyze polysaccharide to a monosaccharide which is then absorbed from the intestine and flows into a blood stream. In the status of type 2 diabetes mellitus (T2DM), patients exhibit hyperglycemia which raises the risk of cardiovascular disease, renal failure, blindness and neurological disorders.[1] Inhibition of polysaccharide digestion prevents rapid glucose uptake from the intestine and relaxes the hyperglycemic status caused from food intake. Accordingly, many glycosidase inhibitors are developed or searched for the treatment of T2DM.

For intestinal α-glucosidases, several potent inhibitors are known including deoxynojirimycin (DNJ),[2] salacinol,[3] miglitol and voglibose.[4] The last two compounds are currently used as a chemical treatment of T2DM. Moreover, numbers of natural compounds are reported as a α-glucosidase inhibitor.[5] On the other hand, not much small

molecule inhibitors are reported for α-amylase. Acarbose, the chemical also used for the treatment of T2DM, is the only widely utilized small molecule inhibitor.[6] Several proteinous inhibitors are known in addition,[7] but instability against gastric condition prohibits their use as a medicine against T2DM. Development of a small molecule α-amylase inhibitor will add an alternative choice for the treatment of T2DM. We here show our approach toward the design and synthesis of small molecule α-amylase inhibitor.

α-Amylase is an enzyme hydrolyzing polysaccharides like starch. Although they are one of a glucosidase family, their substrate recognition is more specific toward a polysaccharide. α-Amylase's binding-site is consisted of several partitions called "sub-site" which individually recognize a sugar unit.[8,9] Each sub-site has relatively low affinity toward the sugar unit, but by recognizing multiple sugar units with multiple sub-sites, α-amylase increases the affinity toward a polysaccharide to enable its specific binding and hydrolysis.[9] This multiple sub-site system prevents a low molecular weight compound to be an efficient inhibitor. Most of glucosidase inhibitors work as an active-site inhibitor by mimicking glucose or its activated state.[10] α-Amylase possesses similar active site with other glucosidase,[9] but the small molecule inhibitors like DNJ only mimics a single glucose unit which gives low affinity toward α-amylase. The small

molecule α-amylase inhibitor acarbose also inhibits the active site of α-amylase by its core structure acarviosine, but it also increases its affinity toward α-amylase by additional sugar units. We think this addition of sugar unit to an active site inhibitor should be the key to develop small molecule α-amylase inhibitor. Accordingly, we designed and synthesized glucose-DNJ conjugate that has DNJ as an active site inhibitor with additional glucose connected through alkyl linker, and tested their inhibitory activity against α-amylase.

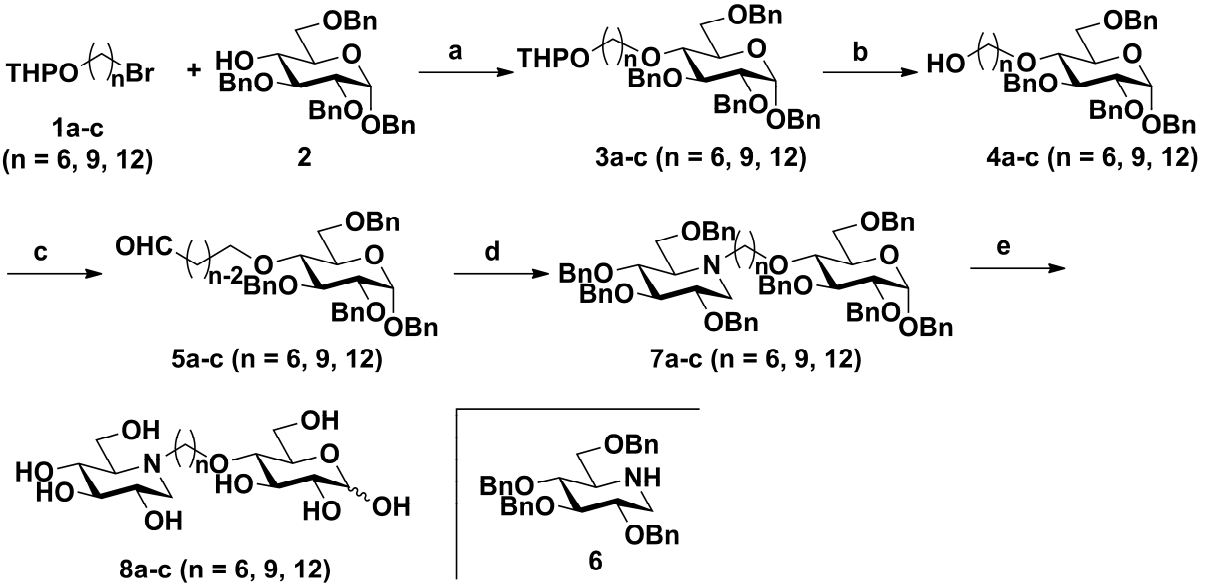
2. Results and discussion

2.1. Synthesis of glucose-DNJ conjugates

We chose two types of glucose-DNJ conjugates (**8a-c**, **13a-f**) to test their α-amylase inhibitory activity. Compounds **8a-c** have a glucose attached through nitrogen atom of DNJ and **13a-f** have a glucose attached through 4-OH group of DNJ prospecting to place the glucose at different sub-site. Also, alkyl linker with various lengths was chosen to give enough flexibility and length to appropriately fit the glucose to a sub-site.

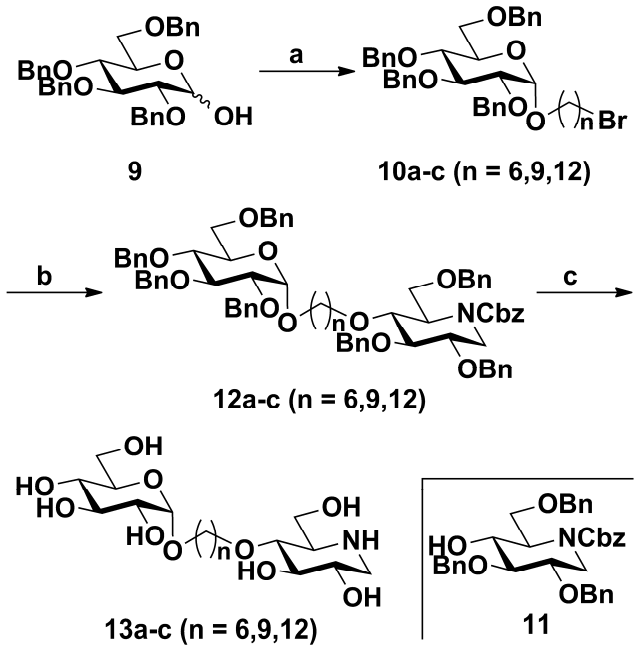
For the synthesis of **8a-c**, benzyl protected DNJ (**6**) was prepared and coupled with glucose-linker conjugate (**5**).[12] 1,2,3,6-tetra-*O*-benzyl-α-D-glucopyranose (**2**) was reacted with alkyl bromide (**1**) to give 4-*O*-bromoalkylated glucose (**3**). After removal of THP group, resulting alcohol (**4**) was oxidized by Dess-Martin periodinane to an aldehyde

(**5**). Aldehyde (**5**) and **6** were then coupled by reductive amination method, and removal of benzyl groups from the resulting conjugate (**7**) gave the product (**8**), that the DNJ and glucose are connected by the alkyl linker which has 6, 9 and 12 atom lengths (Scheme 1).



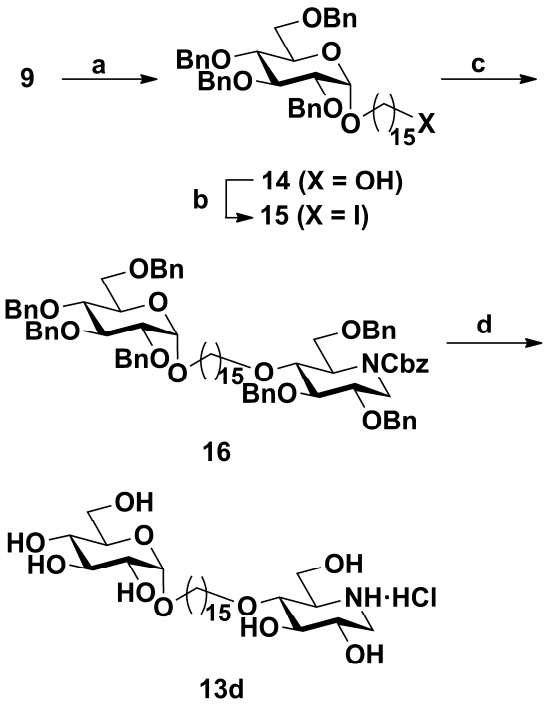
Scheme 1. Reagents and conditions: a) NaH, DMF; b) PPTS, EtOH, 55 °C; c) Dess-Martin periodinane, CH_2Cl_2; d) **6**, $NaBH_3CN$, AcOH, MeOH, CH_2Cl_2; e) Pd/C, H_2, 1 M HCl aq., EtOH

Conjugates **13a-c** were prepared in the following order. 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**9**) was subjected to alpha selective glycosylation with bromoalkyl alcohol to afford **10**.[13] This was then coupled with DNJ (**11**) under basic condition using NaH with DMF as a solvent which gave **12** in a mild yield.[12] Removal of the protective groups from **12** afforded **13a-c** (Scheme 2).



Scheme 2. Reagents and conditions: a) CBr_4, PPh_3, CH_2Cl_2 then TMU, TEAB, bromoalkyl alcohol; b) **11**, NaH, DMF; c) $Pd(OH)_2$, H_2, 1 M HCl aq., THF, EtOH

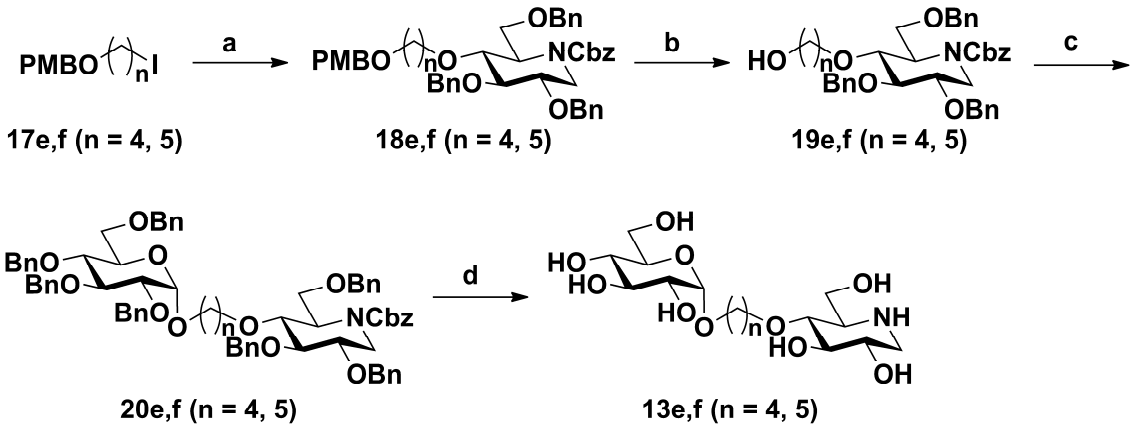
Synthesis of **13d** required modification of a reaction condition, as the same procedure using ω-bromopentadecyl glucoside and **11** with NaH as a base gave no product. To increase the reactivity, the leaving group was replaced from a bromide to an iodide, and as the solubility of **15** in DMF was relatively low compared to **10a-c**, THF was used as a solvent. Using these fixed substrate and solvent, reaction of **15** and **11** was facilitated and gave **16** as a product, which was then applied to a hydrogenation step to remove the protective groups to give **13d** (Scheme 3).



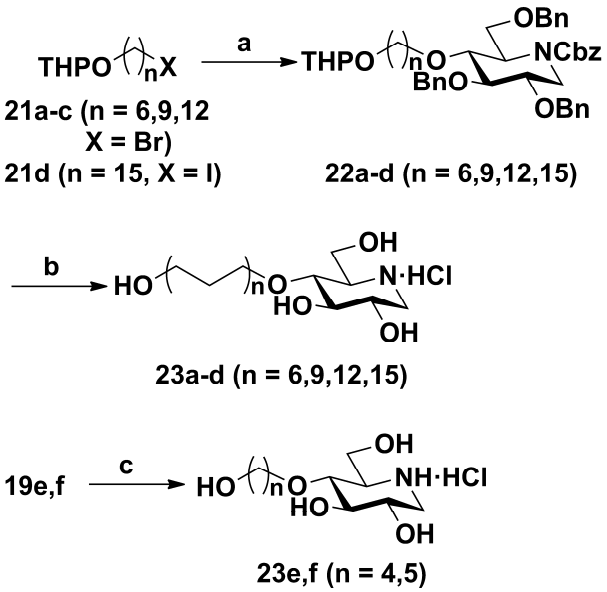
Scheme 3. Reagents and conditions: a) CBr_4, PPh_3, CH_2Cl_2 then TMU, TEAB, 15-hydroxypentadecanol; b) NIS, PPh_3, imidazole, CH_2Cl_2; c) **11**, NaH, THF; d) $Pd(OH)_2$, H_2, 1 M HCl aq., THF, EtOH

Synthesis of **13e** and **13f** also required modification of the reaction, as the reaction of following substrates, 2,3,4,6-tetra-*O*-benzyl-1-*O*- (4-bromobutyl)- α-D-glucopyranose or 2,3,4,6-tetra-*O*-benzyl-1-*O*-(5-bromopentyl)- α-D-glucopyranose, under basic condition, only resulted in the elimination of a bromide. There is a report that bromobutyl glycosides can be utilized as a glycosyl donor by assisting the formation of intramolecular furan ring, which is considered as an activated state.[16] As pyrane ring can also formed stably, bromopentyl glycoside may act in the same manner. So, regarding this intramolecular ring formation as the reason of bromide elimination, we chose to

connect an alkyl linker with DNJ (**11**) before attaching glucose. Alkyl iodide (**17**) was first reacted with **11**, and subsequent removal of PMB group gave **19**. This was then used as a glycosyl acceptor in the alpha selective glycosylation reaction to give **20** as the product. Deprotection of **20** gave **13e,f** (Scheme 4). Also, to ensure the effect of glucose in α-amylase inhibition, compounds **23a-f** were synthesized either by deprotection of the intermediate product or by coupling alkyl halide with **11** (Scheme 5).



Scheme 4. Reagents and conditions: a) **11**, NaH, DMF; b) TFA, CH_2Cl_2; c) 2,3,4,6-tetra-*O*-benzyl-D-glycosyl bromide, TMU, TEAB, CH_2Cl_2; d) $Pd(OH)_2$, H_2, 1 M HCl aq., THF, EtOH



Scheme 5. Reagents and conditions: a) **11**, NaH, THF/DMF, TBAI (for synthesis of **22a-c**); b) PPTS, MeOH then 1 M HCl aq., $Pd(OH)_2$, H_2; c) $Pd(OH)_2$, H_2, 1 M HCl aq., MeOH;

2.2. α-Amylase inhibitory activity of glucose-DNJ conjugates

Initially, **8a-c** and **13a-c** were tested for their α-amylase inhibitory activity to see the effect of an additional glucose attached through different functional group of DNJ. Commercial porcine pancreatic α-amylase was used as an enzyme source and 2,4-dinitrophenyl maltotriose was used as a model substrate for convenient assay procedure.[14] Figure 1 depicts the inhibitory activity of tested compounds at 3 mM. It can be seen that DNJ has only scarce inhibitory activity towards α-amylase. The glucose moiety of the conjugate **8a-c** seems to have no or quite small effect on inhibitory activity. On the other hand, glucose moiety of the conjugates **13a-c** seems to effectively increase

the inhibitory activity of DNJ depending on the length of alkyl linker.

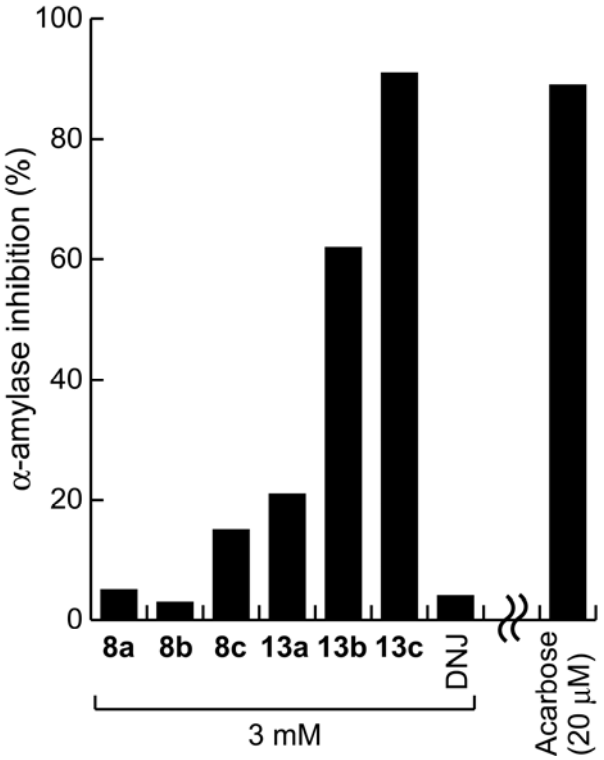


Figure 1. α-Amylase inhibitory activity of **8a-c** and **13a-c** tested at 3 mM. Acarbose (20 μM) was used as a positive control.

The nitrogen atom of DNJ plays a key role in the inhibition of α-glucosidase by giving positive charge at the position resembling the activated state of α-glucoside hydrolysis by α-glucosidase. The small inhibition of **8a-c** may therefore be due to an interfering alkyl chain modifying the nitrogen atom. However, as the similar nitrogen modified compound miglitol retains α-glucosidase inhibitory activity,[4a] the reason of low inhibition compared to **13a-c** is not likely due to this. From the study of α-amylase, the sub-site of the enzyme located at the non-reducing end side contributes more than the

reducing end side in the recognition of the substrate.[15] The result of Figure 1 is matching this fact and indicates the usefulness to attach an additional moiety through 4-OH group of DNJ.

To investigate more about the effect of linker length on α-amylase inhibition, and also to clarify the efficacy of a glucose moiety, we then tested and compared **13a-f** together with **23a-f**. The results are summarized in Table 1. Compound **13a,e,f** and **23a,e,f** had relatively low inhibitory activity and was unable to define IC_{50} value. Therefore these compounds were compared at 5 mM each. And for **13b,c,d** and **23b,c**, IC_{50} values were calculated. Unfortunately, **23d** had low solubility in an assay condition and could not be tested. From the result, the length of linker has a primary effect on α-amylase inhibition, and the inhibition gradually increased by adding an atom to the linker. The most potent was **13c**, and shorter or longer linker gave a compound less inhibitory activity, except the inhibition of **13d** might be decreased due to reduced solubility. The effect of glucose moiety can be seen from the inhibition of **13** and **23**. Regardless of the linker length, addition of glucose moiety increases the inhibitory activity. However, the increase induced by an addition of glucose moiety was not much and far less effective than our primary thoughts and alkyl linker seems to give more effect on inhibition. From the structure of α-amylase, substrate binding site of the

enzyme is surrounded by a hydrophobic surface.[17] The effect of alkyl linker is presumably resulting from a binding to these surface. Glucose moiety itself is hydrophilic but as the top and bottom of the pyranose ring is hydrophobic, it may be contributing somewhat to the affinity. However, the fact that addition of an extra moiety to the small molecule glucosidase inhibitor DNJ increased its inhibition against α-amylase gives us some opportunity to utilize small molecule glucosidase inhibitor against α-amylase by properly designed modification.

Table 1. α-Amylase inhibitory activity of synthetic glucose-DNJ conjugates

	Linker length	Inhibition at 5 mM (%)		IC_{50} (mM)	
	(number of atom)	**13**	**23**	**13**	**23**
e	4	22	12	>5.00	>5.00
f	5	23	19	>5.00	>5.00
a	6	32	25	>5.00	>5.00
b	9	70	64	2.29	3.15
c	12	97	-	0.77	1.20
d	15	-	-	1.12	-
DNJ	0	7		>5.00	

- : unable to define inhibition due to low solubility

3. Conclusion

In conclusion, we have synthesized glucose-DNJ conjugate connected by various length of alkyl linker. Addition of extra glucose through nitrogen atom of DNJ had scarce effect on α-amylase inhibition but addition through 4-OH group increased α-amylase

inhibitory activity. Among the synthesized compounds, the most effective was **13c**, which has dodecyl linker with glucose at the end of linker. The obtained results show an importance of hydrophobic interaction on α-amylase inhibition. Our next target is to utilize this hydrophobic interaction to develop more potent DNJ based α-amylase inhibitor.

4. Experimental Section

4.1. General methods

Porecine pancreatic amylase was purchased from Sigma-Aldrich Co. and 2,4-dinitrophenyl α-maltotriose was synthesized according to the literature.[14] All other commercially available chemicals were purchased from Wako Pure Chem. Ind. Ltd. and used without further purification. Structures of the synthetic compounds were determined by NMR and Mass spectrometry. Bruker AMX500 or Jeol JNM-EX 270 was used to obtain NMR spectrum and either tetramethylsilane (TMS), *tert*-butanol or residual solvent peak was used as an internal standard (^{1}H NMR: TMS 0.00 ppm ($CDCl_3$), CD_3OD 3.30 ppm, *tert*-butanol 1.24 ppm (D_2O); ^{13}C NMR: $CDCl_3$ 77.0 ppm, CD_3OD 49.0 ppm, *tert*-butanol 30.3 ppm (D_2O)). Jeol JMS SX-102A（FAB-MS）or Jeol JMS-T100GCV (FD-MS) or Thermo Scientific Exactive (ESI-MS) was used to obtain mass spectrum. Absorbance was measured by Synergy™ MX (Bio-tech Instruments Inc.,) microplate

reader.

4.2. Synthesis of glucose-DNJ conjugate

*4.2.2. General procedure for the synthesis of **3***

1,2,3,6-tetra-*O*-benzyl-α-D-glucopyranose (**2**, 1 eq.) was dissolved in DMF and 60% NaH (2 eq.) in oil was added at 0 ºC. After stirring the mixture for 30 min. at room temperature (r.t.), **1** (1.2 eq.) dissolved in DMF was added and stirred for 24 hours. The reaction was quenched by adding MeOH and water was added to the resulting solution. The solution was extracted by EtOAc, dried over sodium sulfate and evaporated to dryness. The residue was purified by silica-gel column chromatography to give **3**.

*1,2,3,6-tetra-O-benzyl-4-O-[6-(tetrahydropyranyloxy)hexyl]-α-D-glucopyranose (**3a**)*

Oil, Yield 69%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23-7.39 (20H, m), 4.93 (1H, d, J = 10.8Hz), 4.80 (1H, d, J = 3.5Hz), 4.76 (1H, d, J = 10.8Hz), 4.59-4.69 (3H, m), 4.46-4.54 (4H, m), 3.90 (1H, dd, J = 9.3Hz, 9.3Hz), 3.84 (1H, m), 3.63-3.76 (4H, m), 3.56 (1H, dd, J = 1.9Hz, 10.6Hz), 3.45-3.49 (2H, m), 3.36-3.41 (2H, m), 3.32 (1H, dt, J = 6.7Hz, 9.6Hz), 1.17-1.83 (14H, m), ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.8, 137.1, 128.3, 128.2, 127.74, 127.72, 127.68, 127.64, 127.53, 127.46, 127.3, 98.7, 95.4, 81.9, 79.6, 77.7, 75.5, 73.3, 73.0, 72.8, 70.4, 68.9, 68.3, 67.4, 62.1, 30.6, 30.2, 29.5, 26.0, 25.9, 25.3, 19.5 ppm; $[\alpha]_D^{25}$ +52.0º (c = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found m/z 747.3854,

$C_{45}H_{56}O_8Na^+$ requires *m/z* 747.3867.

1,2,3,6-tetra-O-benzyl-4-O-[9-(tetrahydropyranyloxy)nonyl]-α-D-glucopyranose ***(3b)***

Oil, Yield 89%; ^{1}H-NMR (500 MHz, $CDCl_3$) : 7.23-7.39 (20H, m), 4.93 (1H, d, *J*= 10.8 Hz), 4.80 (1H, d, *J*= 3.6 Hz), 4.77 (1H, d, *J*= 10.8 Hz), 4.47-4.69 (7H, m), 3.91 (1H, dd, *J*= 9.3, 9.3 Hz), 3.86 (1H, m), 3.69-3.77 (3H, m), 3.65 (1H, dd, *J*= 3.7, 10.6 Hz), 3.56 (1H, dd, *J*= 1.9, 10.6Hz), 3.46-3.50 (2H, m), 3.34-3.42 (3H, m), 1.14-1.85 (20H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.8, 137.1, 128.2, 128.1, 127.72, 127.70, 127.63, 127.49, 127.42, 127.31, 98.6, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 73.0, 72.8, 70.4, 68.8, 68.3, 67.5, 62.1, 30.6, 30.2, 29.6, 29.4, 29.31, 29.26, 26.1, 26.0, 25.3, 19.5 ppm; $[\alpha]_D^{25}$ +50.4° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 789.4326, $C_{48}H_{62}O_8Na^+$ requires *m/z* 789.4337.

1,2,3,6-tetra-O-benzyl-4-O-[12-(tetrahydropyranyloxy)dodecyl]-α-D-glucopyranose ***(3c)***

Oil, Yield 80%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23-7.39 (20H, m), 4.93 (1H, d, *J*= 10.8 Hz), 4.80 (1H, d, *J*= 3.6 Hz), 4.77 (1H, d, *J*= 10.8 Hz), 4.47-4.69 (7H, m), 3.91 (1H, dd, *J*= 9.3, 9.3 Hz), 3.85 (1H, m), 3.69-3.77 (3H, m), 3.65 (1H, dd, *J*= 3.7, 10.6 Hz), 3.56 (1H, dd, *J*= 1.9, 10.6 Hz), 3.46-3.50 (2H, m), 3.34-3.42 (3H, m), 1.20-1.84 (26H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.9, 137.1, 128.3, 128.2, 128.1, 127.74, 127.66, 127.53, 127.45, 127.33, 127.31, 98.6, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 73.0, 72.8, 70.4, 68.8, 68.3,

67.5, 62.1, 30.6, 30.3, 29.6, 29.44, 29.40, 29.3, 26.1, 26.0, 25.4, 19.5 ppm; $[\alpha]_D^{25}$ +48.2° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 831.4790, $C_{51}H_{68}O_8Na^+$ requires *m/z* 831.4806.

4.2.3. General procedure for the synthesis of ***4***

Compound **3** (1 eq.) was dissolved in EtOH and PPTS (10 mol%) was added. The solution was stirred for 6 hours at 50 °C, poured in saturated $NaHCO_3$ aq. and extracted by EtOAc. Organic layer was dried over sodium sulfate, evaporated and purified by silica-gel column chromatography to give **4**.

*1,2,3,6-tetra-O-benzyl-4-O-(6-hydroxyhexyl)-α-D-glucopyranose (**4a**)*

Oil, Yield 97%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23-7.39 (20H, m), 4.94 (1H, d, *J*= 10.9 Hz), 4.80 (1H, d, *J*= 3.6 Hz), 4.76 (1H, d, *J*= 10.9 Hz), 4.46-4.69 (6H, m), 3.91 (1H, dd, *J*= 9.5 Hz), 3.70-3.76 (2H, m), 3.64 (1H, dd, *J*= 3.6, 10.5 Hz), 3.56 (1H, m), 3.48 (1H, dd, *J*= 3.6, 9.5 Hz), 3.38-3.42 (2H, m), 1.22-1.54 (8H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.8, 138.0, 137.8, 137.0, 128.3, 128.2, 127.74, 127.66, 127.54, 127.45, 127.32, 95.4, 81.8, 79.5, 77.6, 75.4, 73.2, 72.9, 72.8, 70.3, 68.8, 68.3, 62.5, 32.4, 30.1, 25.8, 25.5 ppm; $[\alpha]_D^{26}$ +67.1° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 663.3292, $C_{40}H_{48}O_7Na^+$ requires *m/z* 663.3292.

*1,2,3,6-tetra-O-benzyl-4-O-(9-hydroxynonyl)-α-D-glucopyranose (**4b**)*

Oil, Yield quant.; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23-7.39 (20H, m), 4.93 (1H, d, *J* = 10.8 Hz), 4.80 (1H, d, *J* = 3.6 Hz), 4.77 (1H, d, *J* = 10.8 Hz), 4.47-4.69 (6H, m), 3.91 (1H, dd, *J* = 9.2, 9.3 Hz), 3.70-3.76 (2H, m), 3.64 (1H, dd, *J* = 3.8, 10.6 Hz), 3.61 (1H, m), 3.56 (1H, dd, *J* = 2.0, 10.6 Hz), 3.48 (1H, dd, *J* = 3.6, 9.6 Hz), 3.37-3.42 (2H, m), 1.17-1.56(14H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.7, 138.0, 137.8, 137.0, 128.2, 128.1, 127.69, 127.68, 127.60, 127.49, 127.40, 127.29, 95.3, 81.8, 79.5, 77.6, 75.4, 73.2, 73.0, 72.8, 70.3, 68.8, 68.3, 62.5, 32.5, 30.2, 29.32, 29.24, 29.17, 25.9, 25.5 ppm; $[\alpha]_D^{26}$ +62.8° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 705.3760, $C_{43}H_{54}O_7Na^+$ requires *m/z* 705.3762.

*1,2,3,6-tetra-O-benzyl-4-O-(12-hydroxydodecyl)-α-D-glucopyranose (**4c**)*

Oil, Yield 91%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.23-7.39 (20H, m), 4.93 (1H, d, *J* = 10.8 Hz), 4.80 (1H, d, *J* = 3.6 Hz), 4.77 (1H, d, *J* = 10.8 Hz), 4.47-4.69 (6H, m), 3.91 (1H, dd, *J* = 9.3, 9.3 Hz), 3.70-3.77 (2H, m), 3.60-3.66 (3H, m), 3.56 (1H, dd, *J* = 2.0, 10.6 Hz), 3.48 (1H, dd, *J* = 3.6, 9.6 Hz), 3.37-3.42 (2H, m), 1.20-1.57 (20H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.8, 138.1, 137.9, 137.1, 128.3, 128.23, 128.19, 127.8, 127.7, 127.6, 127.5, 127.4, 95.5, 82.0, 79.6, 77.7, 75.5, 73.3, 73.2, 72.9, 70.4, 68.9, 68.4, 62.8, 32.7, 30.3, 29.5, 29.3, 26.1, 25.7 ppm; $[\alpha]_D^{26}$ +58.2° (*c* = 1.00, $CHCl_3$) ; HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 747.4236, $C_{46}H_{60}O_7Na^+$ requires *m/z* 747.4231.

4.2.4. General procedure for the synthesis of ***5***

Compound **4** (1 eq.) was dissolved in CH_2Cl_2 and Dess-Martin Periodinane (1.2 eq.) was added at 0 °C. After stirring for 90 min. at r.t., MeOH was added to quench the reaction. To this solution, Et_2O was added and the precipitate was filtered off by passing through the celite pad. Filtrate was evaporated and the residue was purified by silica-gel column chromatography to give **5**.

*1,2,3,6-tetra-O-benzyl-4-O-(6-oxohexyl)-α-D-glucopyranose (**5a**)*

Oil, Yield 82%; ^{1}H-NMR (500 MHz, $CDCl_3$): 9.68 (1H, t, *J* = 1.8 Hz), 7.23-7.40 (20H, m), 4.95 (1H, d, *J* = 11.0 Hz), 4.81 (1H, d, *J* = 3.6 Hz), 4.74 (1H, d, *J* = 11.0 Hz), 4.46-4.70 (6H, m), 3.90 (1H, dd, *J* = 9.3, 9.3 Hz), 3.72 (2H, m), 3.64 (1H, dd, *J* = 3.7, 10.5 Hz), 3.55 (1H, dd, *J* = 2.0, 10.5 Hz), 3.48 (1H, dd, *J* = 3.6, 9.6Hz), 3.35-3.41 (2H, m), 2.31 (2H, dt, *J* = 1.8, 7.4 Hz), 1.52 (2H, m), 1.41 (2H, m), 1.14-1.28 (2H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 202.4, 138.8, 138.0, 137.9, 137.1, 128.3, 128.22, 128.19, 127.80, 127.74, 127.70, 127.64, 127.59, 127.52, 127.37, 95.4, 81.9, 79.6, 77.7, 75.4, 73.3, 72.8, 72.6, 70.3, 68.9, 68.3, 43.6, 30.0, 25.6, 21.8 ppm; $[\alpha]_D^{24}$ +58.1° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 661.3148, $C_{40}H_{46}O_7Na^+$ requires *m/z* 661.3136.

*1,2,3,6-tetra-O-benzyl-4-O-(9-oxononyl)-α-D-glucopyranose (**5b**)*

Oil, Yield 88%; ^{1}H-NMR (500 MHz, $CDCl_3$): 9.73 (1H, t, *J* = 1.8 Hz), 7.23-7.39 (20H, m),

4.93 (1H, d, *J* = 10.9 Hz), 4.81 (1H, d, *J* = 3.7 Hz), 4.76 (1H, d, *J* = 10.9 Hz), 4.47-4.69 (6H, m), 3.91 (1H, dd, *J* = 9.3 Hz), 3.73 (2H, m), 3.64 (1H, dd, *J* = 3.6, 10.6 Hz), 3.56 (1H, dd, *J* = 2.0, 10.6 Hz), 3.48 (1H, dd, *J* = 3.7, 9.6 Hz), 3.40 (2H, m), 2.38 (2H, dt, *J* = 1.8, 7.3 Hz), 1.54-1.61 (2H, m), 1.42 (2H, m), 1.16-1.27 (8H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 202.5, 138.8, 138.0, 137.8, 137.0, 128.2, 128.14, 128.11, 127.71, 127.64, 127.60, 127.49, 127.41, 127.29, 95.4, 81.9, 79.5, 77.6, 75.4, 73.2, 73.0, 72.8, 70.3, 68.8, 68.3, 43.6, 30.1, 29.09, 29.07, 28.9, 25.9, 21.8 ppm; $[\alpha]_D^{25}$ +56.2° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 703.3621, $C_{43}H_{55}O_7Na^+$ requires *m/z* 703.3605.

*1,2,3,6-tetra-O-benzyl-4-O-(12-oxododecyl)-α-D-glucopyranose(**5c**)*

Oil, Yield 97%; ^{1}H-NMR (500 MHz, $CDCl_3$): 9.74 (1H, t, *J* = 1.8 Hz), 7.24-7.40 (20H, m), 4.93 (1H, d, *J* = 10.9 Hz), 4.81 (1H, d, *J* = 3.7 Hz), 4.76 (1H, d, *J* = 10.9 Hz), 4.47-4.70 (6H, m), 3.91 (1H, dd, *J* = 9.3 Hz), 3.73 (2H, m), 3.65 (1H, dd, *J* = 3.6, 10.6 Hz), 3.57 (1H, dd, *J* = 2.0, 10.6 Hz), 3.48 (1H, dd, *J* = 3.7, 9.6 Hz), 3.40 (2H, m), 2.38 (2H, dt, *J* = 1.8, 7.4 Hz), 1.20-1.64 (18H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 202.9, 138.9, 138.1, 137.9, 137.1, 128.36, 128.25, 128.23, 128.21, 127.84, 127.74, 127.72, 127.62, 127.53, 127.42, 95.5, 82.0, 79.6, 77.7, 75.6, 73.4, 73.2, 72.9, 70.4, 68.9, 68.4, 43.8, 30.3, 29.5, 29.4, 29.32, 29.26, 29.1, 26.1, 22.0 ppm; $[\alpha]_D^{25}$ +56.9° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+Na]^+$ Found *m/z* 745.4096, $C_{46}H_{58}O_7Na^+$ requires *m/z* 745.4075.

4.2.5. General procedure for the synthesis of **7**

Compound **5** (1 eq.) and **6** (1.2 eq.) were immersed in MeOH/AcOH (200/1) and CH_2Cl_2 was added until all the components dissolves. The solution was cooled to 0 ºC, 90% $NaBH_3CN$ (2 eq.) was added and stirred for 12 hours at r.t. The reaction mixture was concentrated and purified by preparative TLC (PTLC) to give **7**.

*1,2,3,6-tetra-O-benzyl-4-O-[6-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-benzyloxymethylpiperidino]hexyl]- α-D-glucopyranose (**7a**)*

Oil, Yield 95%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.15-7.44 (40H, m), 4.99 (2H, dd, *J* = 4.0, 10.9 Hz), 4.81-4.91 (5H, m), 4.65-4.74 (5H, m), 4.43-4.59 (6H, m), 3.97 (1H, dd, *J* = 9.2, 9.3 Hz), 3.77-3.82 (2H, m), 3.60-3.71 (5H, m), 3.41-3.55 (5H, m), 3.10 (1H, dd, *J* = 4.8, 11.3 Hz), 2.54-2.69 (2H, m), 2.32 (1H, bd, *J* = 9.4 Hz), 2.25 (1H, dd, *J* = 10.7, 10.8 Hz), 1.09-1.48 (8H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.93, 138.87, 138.48, 138.46, 138.1, 137.9, 137.7, 137.1, 128.3, 128.26, 128.22, 127.82, 127.76, 127.72, 127.62, 127.53, 127.44, 127.42, 127.33, 95.5, 87.3, 82.0, 79.7, 78.48, 78.44, 77.7, 75.5, 75.2, 75.1, 73.4, 73.3, 73.0, 72.9, 72.6, 70.4, 69.0, 68.4, 65.2, 63.5, 54.4, 52.3, 30.4, 27.4, 26.1, 23.4 ppm; $[\alpha]_D^{24}$ +37.5º (*c* = 0.85, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ Found *m/z* 1146.6078, $C_{74}H_{84}O_{10}N^+$ requires *m/z* 1146.6090.

1,2,3,6-tetra-O-benzyl-4-O-[9-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-

*benzyloxymethylpiperidino]nonyl]- α-D-glucopyranose (**7b**)*

Oil, Yield 88%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.12-7.41 (40H, m), 4.95 (2H, d, *J* = 10.9 Hz), 4.77-4.88 (5H, m), 4.61-4.70 (5H, m), 4.40-4.56 (6H, m), 3.93 (1H, dd, *J* = 9.3, 9.3 Hz), 3.72-3.79 (2H, m), 3.57-3.68 (5H, m), 3.53 (1H, dd, *J* = 2.2, 10.4 Hz), 3.50 (1H, dd, *J* = 3.6, 9.6 Hz), 3.45 (1H, dd, *J* = 9.0, 9.0 Hz), 3.39-3.44 (2H, m), 3.08 (1H, dd, *J* = 4.8, 11.3 Hz), 2.52-2.68 (2H, m), 2.29 (1H, dd, *J* = 2.2, 9.5 Hz), 2.22 (1H, dd, *J* = 10.7, 10.8 Hz), 1.08-1.46 (14H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.92, 138.85, 138.47, 138.45, 138.1, 137.9, 137.7, 137.1, 128.3, 128.22, 128.18, 127.78, 127.72, 127.69, 127.58, 127.49, 127.38, 127.29, 95.5, 87.3, 82.0, 79.6, 78.48, 78.42, 77.7, 75.5, 75.2, 75.0, 73.3, 73.1, 73.0, 72.9, 72.6, 70.4, 68.9, 68.4, 65.2, 63.6, 54.4, 52.3, 30.3, 29.5, 29.4, 27.4, 26.1, 23.4 ppm; $[\alpha]_D^{24}$ +32.1° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ Found *m/z* 1188.6549, $C_{77}H_{90}O_{10}N^+$ requires *m/z* 1188.6559.

*1,2,3,6-tetra-O-benzyl-4-O-[12-[(2R,3R,4R,5S)-3,4,5-tribenzyloxy-2-benzyloxymethylpiperidino]dodecyl]- α-D-glucopyranose (**7c**)*

Oil, Yield 61%; ^{1}H-NMR (500 MHz, $CDCl_3$): 7.15-7.43 (40H, m), 4.97 (2H, d, *J* = 10.9 Hz), 4.80-4.91 (5H, m), 4.63-4.73 (5H, m), 4.43-4.58 (6H, m), 3.96 (1H, dd, *J* = 9.3, 9.3 Hz), 3.75-3.82 (2H, m), 3.59-3.70 (5H, m), 3.56 (1H, dd, *J* = 1.9, 10.4 Hz), 3.52 (1H, dd, *J* = 3.6, 9.6 Hz), 3.42-3.50 (3H, m), 3.12 (1H, dd, *J* = 4.8, 11.3 Hz), 2.56-2.72 (2H, m), 2.32 (1H, dd,

J = 2.2, 9.5 Hz), 2.25 (1H, dd, *J* = 10.8, 10.8 Hz), 1.11-1.49 (20H, m) ppm; ^{13}C-NMR (67.5 MHz, $CDCl_3$): 138.98, 138.91, 138.53, 138.51, 138.2, 138.0, 137.7, 137.2, 128.36, 128.27, 128.24, 128.23, 127.85, 127.78, 127.75, 127.62, 127.54, 127.44, 127.34, 95.5, 87.3, 82.0, 79.7, 78.54, 78.49, 77.8, 75.6, 75.2, 75.1, 73.4, 73.2, 73.0, 72.7, 70.5, 69.0, 68.5, 65.2, 63.6, 54.4, 52.4, 30.4, 29.61, 29.56, 27.5, 26.1, 23.5 ppm; $[\alpha]_D^{24}$ +33.4° (*c* = 1.00, $CHCl_3$); HR-ESI-MS (positive) $[M+H]^+$ Found *m/z* 1230.7013, $C_{80}H_{96}O_{10}N^+$ requires *m/z* 1230.7029.

4.2.6. General procedure for the synthesis of ***8***

Compound **7** was dissolved in EtOH and acidified by 1 M HCl aq. to pH 2. To this solution, 10% Pd on carbon was added and stirred 24 hours under hydrogen atmosphere. The reaction mixture was passed through celite pad, dried under vacuo and purified by LiChrolut® RP-18 (Merck Co.) to afford **8** as a mixture of anomers.

*4-O-[6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-hydroxymethylpiperidino]hexyl]-D-glucopyranose (**8a**)*

Crystal, Yield 54%; β anomer (major), ^{1}H-NMR (500 MHz, D_2O): 4.48 (1H, d, *J* = 8.0 Hz), 3.58-3.79 (5H, m), 3.54 (1H, m), 3.38-3.44 (2H, m), 3.32 (1H, ddd, *J* = 1.9, 5.2, 9.8 Hz), 3.25 (1H, dd, *J* = 9.5, 9.5 Hz), 3.09-3.17 (3H, m), 2.89 (1H, dd, *J* = 4.9, 11.3 Hz), 2.46-2.64 (2H, m), 2.17 (1H, dd, *J* = 11.3, 11.3 Hz), 2.12 (1H, br d, *J* = 9.1 Hz), 1.17-1.47 (8H, m), ppm; ^{13}C-NMR (125 MHz, D_2O): 98.7, 81.2, 80.7, 78.4, 77.9, 77.0, 76.0, 72.9, 71.7, 67.8,

63.3, 60.4, 58.0, 54.8, 31.9, 29.3, 27.9, 25.5 ppm; $[\alpha]_D^{27}$ +26.7° (*c* = 1.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 426.2343, $C_{18}H_{36}NO_{10}^+$ requires *m/z* 426.2339.

*4-O-[9-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-hydroxymethylpiperidino]nonyl]-D-glucopyranose (**8b**)*

Crystal, Yield 37%; β anomer (major), ^{1}H-NMR (500 MHz, D_2O): 4.51 (1H, d, *J* = 7.9 Hz), 3.61-3.82 (5H, m), 3.55 (1H, m), 3.41-3.46 (2H, m), 3.34 (1H, ddd, *J* = 2.1, 5.4, 9.8 Hz), 3.27 (1H, dd, *J* = 9.5, 9.5 Hz), 3.11-3.20 (3H, m), 2.92 (1H, dd, *J* = 4.9, 11.4 Hz), 2.48-2.66 (2H, m), 2.20 (1H, dd, *J* = 11.0, 11.2 Hz), 2.15 (1H, dd, *J* = 2.3, 9.7 Hz), 1.16-1.48 (14H, m) ppm; ^{13}C-NMR (125 MHz, D_2O): 98.7, 81.2, 80.7, 78.4, 77.9, 77.0, 76.1, 73.0, 71.7, 67.8, 63.3, 60.5, 58.1, 54.9, 32.0, 31.3, 31.3, 31.2, 29.5, 27.9, 25.5 ppm; $[\alpha]_D^{27}$ +27.0° (*c* = 2.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 468.2818, $C_{21}H_{42}NO_{10}^+$ requires *m/z* 468.2809

*4-O-[12-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-hydroxymethylpiperidino]dodecyl]-D-glucopyranose (**8c**)*

Crystal, Yield 50%; β anomer (major), ^{1}H-NMR (500 MHz, D_2O): 4.51 (1H, d, *J* = 7.9 Hz), 3.49-3.79 (6H, m), 3.41-3.48 (2H, m), 3.34 (1H, m), 3.31 (1H, dd, *J* = 9.4, 9.4 Hz), 3.12-3.16 (3H, m), 2.90 (1H, dd, *J* = 4.3, 11.0 Hz), 2.52-2.67 (2H, m), 2.19 (1H, dd, *J* = 11.0, 11.0 Hz), 2.11 (1H, bd, *J* = 2.3, 9.8 Hz), 1.15-1.50 (20H, m) ppm; ^{13}C-NMR (125 MHz,

D_2O): 98.7, 81.3, 80.8, 78.7, 78.1, 77.2, 76.1, 72.8, 71.7, 67.9, 63.5, 60.3, 58.6, 55.1, 32.6, 32.3, 32.2, 32.2, 32.2, 32.1, 32.0, 29.5, 28.5, 25.8 ppm; $[\alpha]_D^{27}$ +24.6° (*c* = 1.00, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 510.3271, $C_{24}H_{48}NO_{10}^+$ requires *m/z* 510.3278.

4.2.7. General procedure for the synthesis of ***10***

Compound **9** (1 eq.) was dissolved in CH_2Cl_2 and Ph_3P (4.5 eq.), CBr_4 (4.5 eq.) was added. After stirring for 4 hours, TMU (6.8 eq.), bromoalkyl alcohol (3 eq.) and TEAB (1.2 eq.) was added and further stirred for 12 hours. The reaction mixture was diluted with $CHCl_3$, washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over sodium sulfate, evaporated and purified by silica-gel column chromatography to give **10**.

*2,3,4,6-tetra-O-benzyl-1-O-(6-bromohexyl)-α-D-glucopyranose (**10a**)*

Oil, Yield quant.; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.24 (18H, m), 7.16-7.12 (2H, m), 4.99 (1H, d, *J* = 10.8 Hz), 4.83 (1H, d, *J* = 10.6 Hz), 4.82 (1H, d, *J* = 10.8 Hz), 4.77 (1H, d, *J* = 12.1 Hz), 4.75 (1H, d, *J* = 3.6 Hz), 4.64 (1H, d, *J* = 12.1 Hz), 4.59 (1H, d, *J* = 12.1 Hz), 4.470 (1H, d, *J* = 10.6 Hz), 4.468 (1H, d, *J* = 12.1 Hz), 3.98 (1H, dd, *J* = 9.0, 9.6 Hz), 3.77 (1H, ddd, *J* = 1.9, 3.6, 10.0 Hz), 3.71 (1H, dd, *J* = 3.6, 10.6 Hz), 3.65-3.60 (3H, m), 3.56 (1H, dd, *J* = 3.6, 9.6 Hz), 3.41 (1H, dt, *J* = 9.5, 6.5 Hz), 3.36 (2H, t, *J* = 6.9 Hz), 1.83 (2H, tt, *J* = 6.9, 7.3 Hz), 1.68-1.58 (2H, m), 1.44 (2H, tt, *J* = 7.3, 7.3 Hz), 1.38 (2H, tt, *J* = 7.2, 7.3 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 138.9, 138.3, 138.2, 137.9, 128.33, 128.29

(3C), 127.9, 127.86, 127.82, 127.80, 127.74, 127.60, 127.59, 127.45, 96.9, 82.0, 80.1, 77.7, 75.6, 75.0, 73.4, 73.1, 70.1, 68.5, 67.9, 33.7, 32.6, 29.1, 27.9, 25.3 ppm; $[\alpha]_D^{27}$ +39.0° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 701.2499, $C_{40}H_{46}BrO_6^+$ requires *m/z* 701.2478.

2,3,4,6-tetra-O-benzyl-1-O-(9-bromononyl)-α-D-glucopyranose ***(10b)***

Oil, Yield quant.; ^1H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.24 (18H, m), 7.14-7.12 (2H, m), 4.99 (1H, d, *J* = 10.8 Hz), 4.83 (1H, d, *J* = 10.6 Hz), 4.81 (1H, d, *J* = 10.8 Hz), 4.77 (1H, d, *J* = 12.2 Hz), 4.76 (1H, d, *J* = 3.6 Hz), 4.64 (1H, d, *J* = 12.2 Hz), 4.60 (1H, d, *J* = 12.3 Hz), 4.470 (1H, d, *J* = 10.6 Hz), 4.469 (1H, d, *J* = 12.3 Hz), 3.99 (1H, dd, *J* = 9.3, 9.5 Hz), 3.78 (1H, ddd, *J* = 1.9, 3.7, 10.0 Hz), 3.72 (1H, dd, *J* = 3.7, 10.5 Hz), 3.65-3.60 (3H, m), 3.56 (1H, dd, *J* = 3.6, 9.5 Hz), 3.41 (1H, dt, *J* = 9.8, 6.6 Hz), 3.37 (2H, t, *J* = 6.9 Hz), 1.83 (2H, tt, *J* = 6.9, 7.4 Hz), 1.65-1.59 (2H, m), 1.43-1.27 (10H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 138.9, 138.3, 138.2, 137.9, 128.32, 128.29 (2C), 128.27, 127.92, 127.87, 127.83, 127.80, 127.72, 127.60, 127.58, 127.45, 96.8, 82.1, 80.1, 77.7, 75.6, 75.0, 73.4, 73.0, 70.1, 68.5, 68.1, 33.9, 32.7, 29.32, , 29.26, 29.23, 28.6, 28.1, 26.1 ppm; $[\alpha]_D^{27}$ +36.1° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 743.2980, $C_{43}H_{52}BrO_6^+$ requires *m/z* 743.2947.

2,3,4,6-tetra-O-benzyl-1-O-(12-bromododecyl)-α-D-glucopyranose ***(10c)***

Oil, Yield 94%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.23 (18H, m), 7.17-7.12 (2H, m), 4.99 (1H, d, *J* = 10.6 Hz), 4.83 (1H, d, *J* = 10.7 Hz), 4.81 (1H, d, *J* = 10.6 Hz), 4.77 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 3.6 Hz), 4.64 (1H, d, *J* = 12.0 Hz), 4.60 (1H, d, *J* = 12.2 Hz), 4.47 (1H, d, *J* = 10.7 Hz), 4.46 (1H, d, *J* = 12.2 Hz), 3.99 (1H, dd, *J* = 9.3, 9.6 Hz), 3.78 (1H, ddd, *J* = 2.1, 3.6, 10.0 Hz), 3.72 (1H, dd, *J* = 3.6, 10.6 Hz), 3.65-3.60 (3H, m), 3.56 (1H, dd, *J* = 3.6, 9.6 Hz), 3.42 (1H, dt, *J* = 9.7, 6.6 Hz), 3.37 (2H, t, *J* = 6.9 Hz), 1.82 (2H, tt, *J* = 6.9, 7.2 Hz), 1.65-1.59 (2H, m), 1.43-1.24 (16H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 138.9, 138.3, 138.2, 137.9, 128.28, 128.25 (2C), 128.24, 127.9, 127.81 (2C), 127.77, 127.68, 127.56, 127.54, 127.41, 96.8, 82.0, 80.1, 77.7, 75.6, 75.0, 73.4, 73.0, 70.0, 68.5, 68.1, 33.9, 32.7, 29.5, 29.44, 29.43, 29.33, 29.32 (2C), 28.7, 28.1, 26.1 ppm; $[\alpha]_D^{27}$ +28.1° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 785.3448, $C_{46}H_{58}BrO_6^+$ requires *m/z* 785.3417.

4.2.8. General procedure for the synthesis of ***12***

Compound **10** (1.2 eq.) and **11** (1 eq.) was dissolved in dry DMF. The solution was cooled to 0 °C and NaH (1.5 eq.) was added and stirred under nitrogen atmosphere. After 15 hours, water was added and the solution was extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by PTLC to give **12**.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)hexyloxy] piperidine ***(12a)***

Oil, Yield 61%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.35-7.23 (38H, m), 7.14-7.12 (2H, m), 5.12 (1H, d, J = 12.4 Hz), 5.09 (1H, d, J = 12.4 Hz), 4.98 (1H, d, J = 10.9 Hz), 4.83 (1H, d, J = 10.4 Hz), 4.81 (1H, d, J = 10.9 Hz), 4.76 (1H, d, J = 12.3 Hz), 4.75 (1H, d, J = 3.7 Hz), 4.67 (1H, d, J = 11.5 Hz), 4.65 (1H, d, J = 11.9 Hz), 4.64 (1H, d, J = 12.3 Hz), 4.63 (1H, d, J = 11.5 Hz), 4.59 (1H, d, J = 12.2 Hz), 4.51 (1H, d, J = 11.9 Hz), 4.47 (1H, d, J = 10.8 Hz), 4.45 (1H, d, J = 12.2 Hz), 4.44 (1H, d, J = 11.9 Hz), 4.42 (1H, d, J = 11.9 Hz), 4.10-4.05 (2H, m), 3.98 (1H, dd, J = 9.0, 9.6 Hz), 3.78-3.58 (11H, m), 3.55 (1H, dd, J = 3.7, 9.6 Hz), 3.42-3.37 (2H, m), 3.34 (1H, dd, J = 3.0, 14.2 Hz), 1.58 (2H, tt, J = 7.0, 7.0 Hz), 1.49 (2H, tt, J = 6.5, 6.5 Hz), 1.34-1.23 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 155.7, 138.9, 138.32, 138.30, 138.25, 138.1, 137.9, 136.6, 128.37, 128.36, 128.34, 128.28, 127.93, 127.90, 127.85, 127.82, 127.79, 127.74, 127.70, 127.64, 127.59, 127.56, 127.50, 127.46, 96.8, 82.2, 82.1, 80.1, 78.6, 77.7, 75.6, 75.04, 75.01, 73.4, 73.0 (2C), 72.9, 71.6, 70.6, 70.1, 68.5 (2C), 68.1, 67.1, 56.0, 41.5, 30.0, 29.3, 26.02, 25.95 ppm; $[\alpha]_D^{27}$ +25.7° (c = 0.60, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found m/z 1188.5818, $C_{75}H_{82}NO_{12}^+$ requires m/z 1188.5837

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[9-(2,3,4,6-

*tetra-O-benzyl-α-D-glucopyranosyloxy)nonyloxy] piperidine (**12b**)*

Oil, Yield 34%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.22 (38H, m), 7.17-7.11 (2H, m), 5.12 (1H, d, J = 12.4 Hz), 5.08 (1H, d, J = 12.4 Hz), 4.99 (1H, d, J = 10.9 Hz), 4.83 (1H, d, J = 10.9 Hz), 4.81 (1H, d, J = 10.9 Hz), 4.77 (1H, d, J = 12.0 Hz), 4.76 (1H, d, J = 3.5 Hz), 4.68 (1H, d, J = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz), 4.64 (1H, d, J = 12.0 Hz), 4.63 (1H, d, J = 11.5 Hz), 4.60 (1H, d, J = 12.2 Hz), 4.51 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 10.9 Hz), 4.46 (1H, d, J = 12.2 Hz), 4.44 (1H, d, J = 11.5 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.10-4.05 (2H, m), 3.99 (1H, dd, J = 9.2, 9.4 Hz), 3.80-3.59 (11H, m), 3.56 (1H, dd, J = 3.5, 9.4 Hz), 3.45-3.39 (2H, m), 3.34 (1H, dd, J = 2.4, 14.6 Hz), 1.61 (2H, tt, J = 7.2, 7.2 Hz), 1.51-1.47 (2H, m), 1.34-1.20 (10H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 155.7, 138.9, 138.31, 138.30, 138.2, 138.1, 137.9, 136.6, 128.34, 128.32, 128.28, 128.25, 127.9, 127.84, 127.80, 127.76, 127.72, 127.69, 127.58, 127.53, 127.48, 127.46, 96.8, 82.3, 82.1, 80.1, 78.6, 77.8, 75.6, 75.0, 73.4, 73.0, 72.9, 71.7, 70.6, 70.0, 68.5, 68.2, 67.1, 56.0, 41.5, 30.0, 29.48, 29.45, 29.40, 29.38, 26.12, 26.06 ppm; $[\alpha]_D^{27}$ +23.6° (c = 0.52, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found m/z 1230.6293, $C_{78}H_{88}NO_{12}^+$ requires m/z 1230.6307

*(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[12-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)dodecyloxy] piperidine (**12c**)*

Oil, Yield 31%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.24 (38H, m), 7.14-7.12 (2H, m), 5.12 (1H, d, *J* = 12.4 Hz), 5.09 (1H, d, *J* = 12.4 Hz), 4.99 (1H, d, *J* = 10.9 Hz), 4.83 (1H, d, *J* = 10.8 Hz), 4.81 (1H, d, *J* = 10.9 Hz), 4.77 (1H, d, *J* = 12.1 Hz), 4.76 (1H, d, *J* = 3.5 Hz), 4.68 (1H, d, *J* = 11.5 Hz), 4.65 (1H, d, *J* = 12.0 Hz), 4.64 (1H, d, *J* = 12.1 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.60 (1H, d, *J* = 12.1 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.47 (1H, d, *J* = 10.8 Hz), 4.46 (1H, d, *J* = 12.1 Hz), 4.44 (1H, d, *J* = 12.0 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.10-4.05 (2H, m), 3.99 (1H, dd, *J* = 9.3, 9.6 Hz), 3.80-3.59 (11H, m), 3.55 (1H, dd, *J* = 3.5, 9.6 Hz), 3.44-3.39 (2H, m), 3.34 (1H, dd, *J* = 3.5, 14.2 Hz), 1.62 (2H, tt, *J* = 7.2, 7.2 Hz), 1.51-1.46 (2H, m), 1.37-1.20 (16H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 155.7, 138.9, 138.34, 138.32, 138.26, 138.1, 137.9, 136.6, 128.36, 128.33, 128.29, 128.27, 127.9, 127.846, 127.81, 127.77, 127.72, 127.71, 127.61, 127.58, 127.54, 127.49, 127.47, 96.8, 82.3, 82.1, 80.1, 78.6, 77.8, 75.6, 75.0, 73.4, 73.0, 72.9, 71.7, 70.6, 70.1, 68.5, 68.2, 67.1, 56.0, 41.5, 30.0, 29.6, 29.58, 29.56, 29.49, 29.44, 29.38, 26.14, 26.08 ppm; $[\alpha]_D^{27}$ +23.4° (*c* = 0.48, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 1272.6795, $C_{81}H_{94}NO_{12}^+$ requires *m/z* 1272.6776

4.2.9. General procedure for the synthesis of ***13***

Compound **12** was dissolved in EtOH/THF (2/1) and acidified by 1 M HCl aq. to pH 2. To this solution $Pd(OH)_2$ was added and stirred under hydrogen atmosphere. After 15 hours,

the reaction mixture was passed through celite pad, evaporated and purified by LiCholut RP-18 (Merck Co.) to give **13**.

*(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[6-(α-D-glucopyranosyloxy)hexyloxy]piperidine hydrochloride (**13a**)*

Crystal, Yield 89%; ^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.76 (1H, d, *J* = 3.6 Hz), 3.95-3.90 (1H, m), 3.88 (1H, br d, *J* = 11.4 Hz), 3.83 (1H, dd, *J* = 3.7, 11.4 Hz), 3.79 (1H, dd, *J* = 2.0, 11.8 Hz), 3.75-3.70 (1H, m), 3.69-3.59 (4H, m), 3.55 (1H, ddd, *J* = 2.0, 5.5, 9.5 Hz), 3.48-3.42 (2H, m), 3.38 (1H, dd, *J* = 3.6, 9.5 Hz), 3.35 (1H, dd, *J* = 9.2, 9.2 Hz), 3.35-3.29 (1H, m), 3.28 (1H, dd, *J* = 9.5, 9.5 Hz), 3.13-3.08 (1H, m), 2.86 (1H, dd, *J* = 11.7, 11.7 Hz), 1.68-1.56 (4H, m), 1.46-1.36 (4H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.1, 81.4, 80.8, 75.1, 73.9, 73.7, 73.6, 73.1, 71.9, 69.0, 62.75, 62.67, 62.4, 51.0, 31.3, 30.6, 27.2, 27.0 ppm; $[\alpha]_D^{26}$ +59.6° (*c* = 0.49, MeOH); HR-FAB-MS (negative): $[M-H]^-$ Found *m/z* 424.2186, $C_{18}H_{34}NO_{10}^-$ requires *m/z* 424.2183.

*(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[9-(α-D-glucopyranosyloxy)nonyloxy]piperidine hydrochloride (**13b**)*

Crystal, Yield 77%; ^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.76 (1H, d, *J* = 3.6 Hz), 3.92 (1H, dt, *J* = 8.9, 6.7 Hz), 3.86 (1H, dd, *J* = 3.1, 11.7 Hz), 3.82 (1H, dd, *J* = 4.7, 11.7 Hz), 3.78 (1H, dd, *J* = 2.4, 11.9 Hz), 3.72 (1H, dt, *J* = 9.6, 6.8 Hz), 3.69-3.64 (2H, m), 3.63 (1H, dd,

J = 9.1, 9.6 Hz), 3.60 (1H, dt, J = 8.9, 6.7 Hz), 3.56 (1H, ddd, J = 2.4, 5.5, 9.9 Hz), 3.46 (1H, dd, J = 9.0, 9.0 Hz), 3.43 (1H, dt, J = 9.6, 6.5 Hz), 3.38 (1H, dd, J = 3.6, 9.6 Hz), 3.34 (1H, dd, J = 9.0, 10.2 Hz), 3.31 (1H, dt, J = 4.8, 11.9 Hz), 3.28 (1H, dd, J = 9.1, 9.9 Hz), 3.09 (1H, ddd, J = 3.1, 4.7, 10.2 Hz), 2.84 (1H, dd, J = 11.9, 11.9 Hz), 1.68-1.54 (4H, m), 1.42-1.30 (10H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.1, 78.4, 77.3, 75.1, 74.5, 73.62, 73.57, 71.8, 69.1, 68.8, 62.7, 61.1, 58.7, 47.4, 31.2, 30.6, 30.5, 27.3, 27.1 ppm; $[\alpha]_D^{26}$ +61.4° (c = 0.33, MeOH); HR-FAB-MS (negative): $[M-H]^-$ Found m/z 466.2641, $C_{21}H_{40}NO_{10}^-$ requires m/z 466.2652.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[12-(α-D-glucopyranosyloxy)dodecyloxy]piperidine hydrochloride ***(13c)***

Crystal, Yield 78%; ^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.76 (1H, d, J = 3.6 Hz), 3.92 (1H, dt, J = 9.0, 6.4 Hz), 3.86 (1H, dd, J = 2.4, 12.0 Hz), 3.82 (1H, dd, J = 4.2, 12.0 Hz), 3.78 (1H, dd, J = 2.3, 11.8 Hz), 3.71 (1H, dt, J = 9.5, 6.9 Hz), 3.70-3.64 (2H, m), 3.63 (1H, dd, J = 9.6, 9.7 Hz), 3.62-3.58 (1H, m), 3.56 (1H, ddd, J = 2.4, 5.5, 9.6 Hz), 3.46 (1H, dd, J = 9.2, 9.2 Hz), 3.43 (1H, dt, J = 9.7, 6.4 Hz), 3.38 (1H, dd, J = 3.6, 9.7 Hz), 3.34 (1H, dd, J = 9.2, 10.0 Hz), 3.31 (1H, dt, J = 4.8, 11.8 Hz), 3.28 (1H, dd, J = 9.6, 9.6 Hz), 3.11-3.07 (1H, m), 2.84 (1H, dd, J = 11.8, 11.8 Hz), 1.66-1.53 (4H, m), 1.42-1.26 (16H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.1, 78.4, 77.3, 75.1, 74.6, 73.60, 73.57, 71.8, 69.1, 68.8, 62.7,

61.1, 58.7, 47.4, 31.2, 30.7, 30.61, 30.56, 27.3, 27.1 ppm; $[\alpha]_D^{27}$ +67.1° (*c* = 0.17, MeOH); HR-FAB-MS (negative): $[M-H]^-$ Found *m/z* 508.3136, $C_{24}H_{46}NO_{10}^-$ requires *m/z* 508.3122.

*4.2.10. Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-(15-hydroxypentadecyl) -α-D-glucopyranose (**14**)*

Compound **9** (204.9 mg, 0.379 mmol) was dissolved in CH_2Cl_2 (4 mL) and Ph_3P (294.9 mg, 1.12 mmol), CBr_4 (374.3 mg, 1.13 mmol) was added. After stirring for 4 hours, THF (4 mL) solution of TMU (272 μL, 2.27 mmol), 15-hydroxypentadecanol (180.6 mg, 0.74 mmol) and TEAB (95.7 mg, 0.455 mmol) was added and further stirred for 12 hours. The reaction mixture was diluted with 1 M HCl aq. and extracted by EtOAc. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried over sodium sulfate, evaporated and purified by silica-gel column chromatography (Hexane/EtOAc = 9/1 to 3/1) to give **14** (123.6 mg, 43%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.22 (18H, m), 7.15-7.12 (2H, m), 4.99 (1H, d, *J* = 10.8 Hz), 4.83 (1H, d, *J* = 10.8 Hz), 4.81 (1H, d, *J* = 10.8 Hz), 4.76 (1H, d, *J* = 12.1 Hz), 4.76 (1H, d, *J* = 3.7 Hz), 4.64 (1H, d, *J* = 12.1 Hz), 4.59 (1H, d, *J* = 12.1 Hz), 4.47 (1H, d, *J* = 10.8 Hz), 4.45 (1H, d, *J* = 12.1 Hz), 4.00 (1H, dd, *J* = 9.2, 9.2 Hz), 3.79 (1H, ddd, *J* = 1.9, 3.6, 9.9 Hz), 3.72 (1H, dd, *J* = 3.6, 10.7 Hz), 3.66-3.60 (3H, m), 3.56 (1H, dd, *J* = 3.7, 9.2 Hz), 3.55 (2H, t, *J* = 6.7 Hz), 3.42 (1H, dt, *J* = 9.8, 6.7 Hz), 1.63 (2H, tt, *J* = 6.7, 7.0

Hz), 1.51 (2H, tt, J = 6.7, 6.7 Hz), 1.38-1.24 (22H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 138.8, 138.2, 138.1, 137.8, 128.2, 128.1, 127.8, 127.72, 127.69, 127.6, 127.5, 127.3, 96.7, 81.9, 80.0, 77.7, 75.5, 74.9, 73.3, 72.9, 69.9, 68.4, 68.1, 62.6, 32.6, 29.48, 29.45, 29.43, 29.40, 29.27, 29.23, 26.0, 25.9 ppm; $[\alpha]_D^{27}$ +31.1° (c = 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found m/z 765.4725, $C_{49}H_{65}O_7^+$ requires m/z 765.4730.

4.2.11. Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-(15-iodopentadecyl)-α-D-glucopyranose (15)

Compound **14** (123.6 mg, 0.161 mmol) was dissolved in CH_2Cl_2 (3 mL) and Ph_3P (52.6 mg, 0.201 mmol), imidazole (16.6 mg, 0.244 mmol), *N*-iodosuccinimide (60.7 mg, 0.270 mmol) was added. After stirring for an hour, the reaction mixture was evaporated and the residue was purified by silica-gel column chromatography (Hexane/EtOAc = 9/1 to 4/1) to give **15** (86.2 mg, 61%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.24 (18H, m), 7.16-7.12 (2H, m), 4.99 (1H, d, J = 10.7 Hz), 4.83 (1H, d, J = 10.7 Hz), 4.81 (1H, d, J = 10.7 Hz), 4.77 (1H, d, J = 12.0 Hz), 4.76 (1H, d, J = 3.6 Hz), 4.65 (1H, d, J = 12.0 Hz), 4.60 (1H, d, J = 12.1 Hz), 4.47 (1H, d, J = 10.7 Hz), 4.46 (1H, d, J = 12.1 Hz), 3.99 (1H, dd, J = 9.3, 9.5 Hz), 3.78 (1H, ddd, J = 2.0, 3.6, 10.0 Hz), 3.72 (1H, dd, J = 3.6, 10.5 Hz), 3.65-3.60 (3H, m), 3.55 (1H, dd, J = 3.6, 9.5 Hz), 3.42 (1H, dt, J = 9.7, 6.8 Hz), 3.16 (2H, t, J = 7.1 Hz), 1.80 (2H, tt, J = 7.1, 7.1

Hz), 1.62 (2H, tt, *J* = 6.8, 6.8 Hz), 1.39-1.24 (22H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 138.9, 138.3, 138.2, 137.9, 128.30, 128.26, 127.92, 127.83, 127.78, 127.69, 127.56, 127.55, 127.42, 96.8, 82.1, 80.1, 77.8, 75.6, 75.0, 73.4, 73.0, 70.0, 68.5, 68.2, 33.5, 30.4, 29.58, 29.56, 29.54, 29.49, 29.47, 29.37, 29.34, 28.5, 26.1, 7.2 ppm; $[\alpha]_D^{27}$ +25.3° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 875.3770, $C_{49}H_{64}IO_6^+$ requires *m/z* 875.3748.

*4.2.12. Synthesis of (2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[15-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pentadecyloxy] piperidine (**16**)*

Compound **15** (441.8 mg, 0.503 mmol) and **11** (224.1 mg, 0.395 mmol) was dissolved in dry THF. The solution was cooled to 0 °C and NaH (21.4 mg, 0.892 mmol) was added and stirred under argon atmosphere. After 17 hours, water was added and the solution was extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 4/1) to give **16** (62.8 mg, 12%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.24 (38H, m), 7.14-7.12 (2H, m), 5.12 (1H, d, *J* = 12.4 Hz), 5.09 (1H, d, *J* = 12.4 Hz), 4.99 (1H, d, *J* = 10.8 Hz), 4.83 (1H, d, *J* = 10.7 Hz), 4.81 (1H, d, *J* = 10.8 Hz), 4.77 (1H, d, *J* = 12.0 Hz), 4.76 (1H, d, *J* = 3.6 Hz), 4.68 (1H, d,

J = 11.6 Hz), 4.65 (1H, d, *J* = 11.7 Hz), 4.64 (1H, d, *J* = 12.0 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 12.2 Hz), 4.51 (1H, d, *J* = 12.0 Hz), 4.47 (1H, d, *J* = 10.7 Hz), 4.46 (1H, d, *J* = 12.2 Hz), 4.44 (1H, d, *J* = 11.7 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.11-4.05 (2H, m), 3.99 (1H, dd, *J* = 9.3, 9.6 Hz), 3.80-3.59 (11H, m), 3.56 (1H, dd, *J* = 3.6, 9.6 Hz), 3.44-3.39 (2H, m), 3.34 (1H, dd, *J* = 3.2, 14.3 Hz), 1.66-1.59 (2H, m), 1.53-1.46 (2H, m), 1.40-1.20 (22H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): 172.4, 155.7, 138.9, 138.31, 138.29, 138.23, 138.1, 137.9, 136.6, 128.35, 128.32, 128.29, 128.26, 128.0, 127.85, 127.81, 127.77, 127.73, 127.71, 127.65, 127.6, 127.53, 127.48, 127.46, 96.8, 82.3, 82.1, 80.1, 78.6, 77.7, 75.6, 75.00, 74.97, 73.4, 73.0, 72.9, 71.7, 70.6, 70.0, 68.5, 68.2, 67.1, 56.0, 41.4, 30.0, 29.65, 29.62, 29.58, 29.55, 29.47, 29.41, 29.35, 26.12, 26.06 ppm; $[\alpha]_D^{27}$ +21.3° (*c* = 0.75, $CHCl_3$); HR-FD-MS (positive): fragment ion $[M-H]^+$ Found *m/z* 1314.7247, $C_{84}H_{100}NO_{12}^+$ requires *m/z* 1314.7246

*4.2.13. Synthesis of (2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[15-(α-D-glucopyranosyloxy)pentadecyloxy]piperidine hydrochloride (**13d**)*

Protective groups of **16** (51.7 mg, 0.0393 mmol) was removed by the method written in §4.2.9 to give **13d** (19.4 mg, 74%) as a crystal.

^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.76 (1H, d, *J* = 3.6 Hz), 3.92 (1H, dt, *J* = 8.9, 6.6 Hz), 3.85 (1H, dd, *J* = 3.1, 11.8 Hz), 3.81 (1H, dd, *J* = 4.6, 11.8 Hz), 3.78 (1H, dd, *J* = 2.1, 12.0

Hz), 3.72 (1H, dt, *J* = 9.6, 7.0 Hz), 3.68-3.59 (4H, m), 3.56 (1H, ddd, *J* = 2.1, 5.5, 9.6 Hz), 3.45 (1H, dd, *J* = 9.0, 9.0 Hz), 3.45-3.40 (1H, m), 3.38 (1H, dd, *J* = 3.6, 9.6 Hz), 3.33 (1H, dd, *J* = 9.0, 10.2 Hz), 3.33-3.28 (1H, m), 3.28 (1H, dd, *J* = 9.6, 9.6 Hz), 3.08 (1H, ddd, *J* = 3.1, 4.6, 10.2 Hz), 2.84 (1H, dd, *J* = 12.0, 12.0 Hz), 1.67-1.53 (4H, m), 1.42-1.26 (22H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.1, 78.4, 77.3, 75.1, 74.6, 73.6, 73.5, 71.8, 69.1, 68.8, 62.7, 61.0, 58.7, 47.3, 31.2, 30.71, 30.68, 30.61, 30.58, 27.3, 27.1 ppm; $[\alpha]_D^{26}$ +49.9º (*c* = 0.63, MeOH); HR-FAB-MS (negative): $[M-H]^-$ Found *m/z* 550.3555, $C_{27}H_{52}NO_{10}^-$ requires *m/z* 550.3591.

4.2.14. General procedure for the synthesis of ***18***

Compound **17** (1.5 eq.) and **11** (1 eq.) were dissolved in DMF and NaH (4 eq.) was added. The mixture was stirred for 15 hours under argon atmosphere and then sat. NH_4Cl aq. was added and extracted by EtOAc. Organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography to give **18**.

*(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[4-(p-methoxybenzyloxy)butyloxy]piperidine (**18e**)*

Oil, Yield 30%; ^{1}H NMR (270 MHz, $CDCl_3$, r.t.): 7.34-7.25 (22H, m), 6.86 (2H, d, *J* = 8.6 Hz), 5.13 (1H, d, *J* = 12.4 Hz), 5.07 (1H, d, *J* = 12.4 Hz), 4.66 (1H, d, *J* = 11.6 Hz), 4.64

(1H, d, *J* = 11.6 Hz), 4.61 (1H, d, *J* = 11.6 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 4.43 (1H, d, *J* = 11.6 Hz), 4.41 (1H, d, *J* = 12.0 Hz), 4.38 (2H, s), 4.10-4.04 (2H, m), 3.78 (3H, s), 3.76-3.62 (6H, m), 3.46-3.29 (4H, m), 1.63-1.54 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 159.0, 155.7, 138.3, 138.0, 136.6, 130.7, 129.2, 128.4, 128.3, 127.86, 127.82, 127.76, 127.64, 127.60, 127.54, 127.51, 113.7, 82.1, 78.6, 75.0, 73.0, 72.9, 72.5, 71.4, 70.6, 69.8, 68.5, 67.2, 56.0, 55.2, 41.4, 26.8, 26.4 ppm; $[\alpha]_D^{27}$ +13.6° (*c* = 2.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 759.3785, $C_{47}H_{53}NO_8^+$ requires *m/z* 759.3771.

*(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[5-(p-methoxybenzyloxy)pentyloxy] piperidine (**18f**)*

Oil, Yield 46%; ^{1}H NMR (270 MHz, $CDCl_3$, r.t.): 7.33-7.21 (22H, m), 6.85 (2H, d, *J* = 8.6 Hz), 5.13 (1H, d, *J* = 12.5 Hz), 5.08 (1H, d, *J* = 12.5 Hz), 4.67 (1H, d, *J* = 11.6 Hz), 4.64 (1H, d, *J* = 11.7 Hz), 4.62 (1H, d, *J* = 11.6 Hz), 4.50 (1H, d, *J* = 12.1 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.42 (1H, d, *J* = 12.1 Hz), 4.40 (2H, s), 4.12-4.05 (2H, m), 3.76 (3H, s), 3.76-3.63 (6H, m), 3.46-3.29 (4H, m), 1.61-1.45 (4H, m), 1.38-1.29 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 159.0, 155.7, 138.24, 138.21, 138.0, 136.6, 130.7, 129.1, 128.3, 128.2, 127.80, 127.76, 127.69, 127.62, 127.58, 127.53, 127.48, 127.47, 113.7, 82.1, 78.5, 74.9, 73.0, 72.9, 72.4, 71.5, 70.5, 69.9, 68.5, 67.1, 55.9, 55.2, 41.4, 29.8, 29.5, 22.7 ppm; $[\alpha]_D^{27}$ +11.9° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 773.3922, $C_{48}H_{55}NO_8^+$

requires *m/z* 773.3928

4.2.15. General procedure for the synthesis of ***19***

Compound **18** was dissolved in 10% TFA/CH_2Cl_2 and stirred for 2 hours. The reaction mixture was evaporated and the residue was purified by PTLC to give **19**.

*(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-(4-hydroxybutyloxy)piperidine (**19e**)*

Oil, Yield 66%; ^{1}H NMR (270 MHz, $CDCl_3$, r.t.): 7.34-7.23 (20H, m), 5.15 (1H, d, *J* = 12.4 Hz), 5.09 (1H, d, *J* = 12.4 Hz), 4.63 (1H, d, *J* = 11.9 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 4.58 (1H, d, *J* = 11.9 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.42 (1H, d, *J* = 11.8 Hz), 4.42 (1H, d, *J* = 12.0 Hz), 4.24 (1H, dd, *J* = 4.7, 9.0 Hz), 4.14 (1H, br d, *J* = 14.4 Hz), 3.74-3.59 (6H, m), 3.55-3.44 (3H, m), 3.28 (1H, dd, *J* = 3.0, 14.4 Hz), 1.61-1.50 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 155.8, 138.1, 138.0, 137.9, 136.6, 128.33, 128.28, 128.25, 128.23, 127.80, 127.78, 127.73, 127.59, 127.52, 127.50, 80.5, 76.95, 74.7, 72.9, 72.7, 71.1, 70.4, 68.1, 67.1, 62.2, 55.1, 40.4, 29.7, 26.4 ppm; $[\alpha]_D^{27}$ +10.3° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 639.3193, $C_{39}H_{45}NO_7^+$ requires *m/z* 639.3196.

*(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-(5-hydroxypentyloxy)piperidine (**19f**)*

Oil, Yield quant.; ^{1}H NMR (270 MHz, $CDCl_3$, r.t.): 7.40-7.23 (20H, m), 5.11 (2H, s), 4.66

(1H, d, J = 11.8 Hz), 4.64 (1H, d, J = 11.8 Hz), 4.62 (1H, d, J = 11.8 Hz), 4.52 (1H, d, J = 12.0 Hz), 4.44 (1H, d, J = 11.8 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.17-4.04 (2H, m), 3.76-3.61 (6H, m), 3.55 (2H, t, J = 6.5 Hz), 3.43 (1H, td, J = 6.5, 9.0 Hz), 3.33 (1H, dd, J = 2.8, 14.5 Hz), 1.62-1.45 (4H, m), 1.38-1.25 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 155.8, 138.2, 138.0, 136.6, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 81.6, 78.1, 74.9, 73.0, 72.8, 71.3, 70.6, 68.4, 67.2, 62.7, 55.7, 41.2, 32.4, 29.6, 22.3 ppm; $[\alpha]_D^{27}$ +7.2° (c = 0.27, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 653.3339, $C_{40}H_{47}NO_7^+$ requires *m/z* 653.3353.

4.2.16. General procedure for the synthesis of ***20***

Compound **9** (1 eq) was dissolved in CH_2Cl_2 and Ph_3P (1.1 eq.), CBr_4 (1.2 eq) was added. After stirring for 14 hours at r.t., CH_2Cl_2 solution of **19** (0.68 eq.), TMU (1.6 eq.) and TEAB (1 eq.) was added and further stirred for 20 hours at 40 ºC. The reaction mixture was diluted with water and extracted by $CHCl_3$. The organic layer was dried over sodium sulfate, evaporated and purified by silica-gel column chromatography to give **20**.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[4-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)butyloxy] piperidine ***(20e)***

Oil, Yield 46%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.35-7.22 (38H, m), 7.14-7.12 (2H, m), 5.12 (1H, d, J = 12.5 Hz), 5.08 (1H, d, J = 12.5 Hz), 4.96 (1H, d, J = 10.8 Hz), 4.82 (1H, d,

J = 10.8 Hz), 4.79 (1H, d, *J* = 10.8 Hz), 4.74 (1H, d, *J* = 12.1 Hz), 4.73 (1H, d, *J* = 3.5 Hz), 4.65 (1H, d, *J* = 11.6 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.62 (1H, d, *J* = 12.1 Hz), 4.61 (1H, d, *J* = 11.6 Hz), 4.59 (1H, d, *J* = 12.2 Hz), 4.49 (1H, d, *J* = 12.4 Hz), 4.46 (1H, d, *J* = 10.8 Hz), 4.44 (1H, d, *J* = 12.2 Hz), 4.43 (1H, d, *J* = 11.5 Hz), 4.42 (1H, d, *J* = 12.4 Hz), 4.10-4.05 (2H, m), 3.96 (1H, dd, *J* = 9.0, 9.6 Hz), 3.75-3.57 (11H, m), 3.54 (1H, dd, *J* = 3.5, 9.6 Hz), 3.45-3.39 (1H, m), 3.37-3.32 (1H, m), 3.33 (1H, dd, *J* = 3.0, 14.4 Hz), 1.64-1.52 (4H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 155.7, 138.8, 138.27, 138.22, 138.0, 137.9, 136.6, 128.36, 128.35, 128.30, 127.95, 127.87, 127.85, 127.80, 127.76, 127.73, 127.61, 127.52, 127.49, 127.47, 96.9, 82.10, 82.06, 80.0, 78.5, 77.6, 75.6, 75.0, 73.4, 73.0, 72.9, 71.3, 70.5, 70.1, 68.5, 68.4, 67.9, 67.1, 55.9, 41.3, 26.8, 26.2 ppm; $[\alpha]_D^{27}$ +16.5° (*c* = 0.19, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 1161.5569, $C_{73}H_{79}NO_{12}^+$ requires *m/z* 1161.5602.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[5-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)pentyloxy] piperidine ***(20f)***

Oil, Yield 59%; ^{1}H NMR (500 MHz, $CDCl_3$, r.t.): 7.36-7.22 (38H, m), 7.16-7.11 (2H, m), 5.12 (1H, d, *J* = 12.3 Hz), 5.08 (1H, d, *J* = 12.3 Hz), 4.97 (1H, d, *J* = 10.9 Hz), 4.82 (1H, d, *J* = 10.8 Hz), 4.79 (1H, d, *J* = 10.9 Hz), 4.76 (1H, d, *J* = 12.1 Hz), 4.73 (1H, d, *J* = 3.6 Hz), 4.66 (1H, d, *J* = 11.7 Hz), 4.64 (1H, d, *J* = 11.7 Hz), 4.63 (1H, d, *J* = 12.1 Hz), 4.62 (1H, d, *J* = 11.7 Hz), 4.59 (1H, d, *J* = 12.1 Hz), 4.50 (1H, d, *J* = 12.1 Hz), 4.46 (1H, d, *J* = 10.8 Hz),

4.45 (1H, d, J = 12.1 Hz), 4.44 (1H, d, J = 11.7 Hz), 4.42 (1H, d, J = 12.1 Hz), 4.10-4.04 (2H, m), 3.97 (1H, dd, J = 9.3, 9.3 Hz), 3.76-3.56 (11H, m), 3.54 (1H, dd, J = 3.6, 9.6 Hz), 3.44-3.33 (2H, m), 3.33 (1H, dd, J = 2.7, 14.5 Hz), 1.62-1.46 (4H, m), 1.37-1.24 (2H, m) ppm; ^{13}C NMR (67.5 MHz, $CDCl_3$, r.t.): 155.7, 138.9, 138.8, 138.32, 138.29, 138.25, 138.1, 137.9, 136.6, 128.4, 128.3, 128.0, 127.93, 127.90, 127.84, 127.76, 127.6, 127.5, 96.9, 82.2, 82.1, 80.0, 78.6, 77.7, 75.7, 75.1, 75.0, 73.5, 73.10, 73.07, 72.96, 71.5, 70.6, 70.1, 68.51, 68.46, 68.1, 67.2, 56.0, 41.5, 29.9, 29.3, 22.6 ppm; $[\alpha]_D^{27}$ +24.6° (c = 0.54, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found m/z 1175.5759, $C_{74}H_{81}NO_{12}^+$ requires m/z 1175.5759.

4.2.17. Synthesis of ***13e,f***

Protective groups of **20** was removed by the method written in §4.2.9 to give **13e** or **13f**.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[4-(α-D-glucopyranosyloxy)butyloxy]piperidine hydrochloride ***(13e)***

Crystal, Yield 81%; ^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.77 (1H, d, J = 3.6 Hz), 4.00-3.90 (1H, m), 3.86 (1H, br d, J = 11.6 Hz), 3.83 (1H, br d, J = 11.6 Hz), 3.79 (1H, dd, J = 2.0, 11.8 Hz), 3.78-3.74 (1H, m), 3.69-3.63 (3H, m), 3.62 (1H, dd, J = 9.3, 9.6 Hz), 3.56 (1H, ddd, J = 2.0, 5.5, 9.5 Hz), 3.49-3.43 (2H, m), 3.38 (1H, dd, J = 3.6, 9.6 Hz), 3.37-3.34 (1H, m), 3.33-3.28 (1H, m), 3.27 (1H, dd, J = 9.3, 9.5 Hz), 3.12-3.07 (1H, m), 2.84 (1H, dd, J = 11.8, 11.8 Hz), 1.74-1.68 (4H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.1, 78.4, 77.2,

75.1, 74.2, 73.7, 73.5, 71.9, 68.84, 68.78, 62.8, 61.0, 58.7, 47.4, 28.0, 27.2 ppm; $[\alpha]_D^{26}$ +59.4° (*c* = 0.14, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 398.2005, $C_{16}H_{32}NO_{10}^+$ requires *m/z* 398.2026

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-[5-(α-D-glucopyranosyloxy)pentyloxy]piperidine hydrochloride ***(13f)***

Crystal, Yield 85%; ^{1}H NMR (500 MHz, CD_3OD, r.t.): 4.76 (1H, d, *J* = 3.8 Hz), 3.94 (1H, td, *J* = 6.3, 9.0 Hz), 3.85 (1H, dd, *J* = 3.2, 11.7 Hz), 3.82 (1H, dd, *J* = 4.6, 11.7 Hz), 3.79 (1H, dd, *J* = 2.2, 11.8 Hz), 3.74 (1H, td, *J* = 6.6, 9.5 Hz), 3.68-3.60 (4H, m), 3.57 (1H, ddd, *J* = 2.2, 5.7, 9.8 Hz), 3.46 (1H, dd, *J* = 9.0, 9.0 Hz), 3.45 (1H, td, *J* = 6.2, 9.5 Hz), 3.38 (1H, dd, *J* = 3.8, 9.8 Hz), 3.28 (1H, dd, *J* = 9.0, 10.3 Hz), 3.32-3.28 (1H, m), 3.27 (1H, dd, *J* = 8.9, 9.8 Hz), 3.09 (1H, ddd, *J* = 3.2, 4.6, 10.3 Hz), 2.84 (1H, dd, *J* = 11.9, 11.9 Hz), 1.72-1.58 (4H, m), 1.57-1.41 (2H, m) ppm; ^{13}C NMR (125 MHz, CD_3OD, r.t.): 100.0, 78.4, 77.3, 75.1, 74.4, 73.7, 73.6, 71.9, 68.89, 68.84, 62.8, 61.0, 58.8, 47.3, 30.9, 30.3, 23.9 ppm; $[\alpha]_D^{26}$ +65.4° (*c* = 0.25, MeOH); HR-FAB-MS (negative): $[M-H]^-$ Found *m/z* 410.2005, $C_{17}H_{32}NO_{10}^-$ requires *m/z* 410.2026.

4.2.18. General procedure for the synthesis of ***22a-c***

Compound **21** (2 eq.) and **11** (1eq.) was dissolved in THF/DMF (1/1) and TBAI (1 eq.), NaH (4 eq.) was added. After stirring for 12 hours, sat. NH_4Cl aq. was added and

extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography to give **22a-c**.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[6-(tetrahydropyran-2-yloxy)hexyloxy] piperidine ***(22a)***

Oil, Yield 64%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 7.35-7.23 (20H, m), 5.13 (1H, d, J= 12.5 Hz), 5.08 (1H, d, J= 12.5 Hz), 4.68 (1H, d, J= 11.5 Hz), 4.64 (1H, d, J= 11.8 Hz), 4.62 (1H, d, J= 11.5 Hz), 4.55 (1H, dd, J= 2.8, 4.2 Hz), 4.52 (1H, d, J= 11.9 Hz), 4.44 (1H, d, J= 11.8 Hz), 4.42 (1H, d, J= 11.9 Hz), 4.12-4.05 (2H, m), 3.85 (1H, ddd, J= 3.9, 7.0, 11.0 Hz), 3.77-3.61 (7H, m), 3.52-3.30 (4H, m), 1.87-1.42 (10H, m), 1.42-1.21 (6H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 155.6, 138.22, 138.18, 138.0, 136.6, 128.3, 128.2, 127.76, 127.72, 127.65, 127.54, 127.49, 127.43, 126.50, 98.7, 82.1, 78.5, 74.9, 73.0, 72.9, 71.6, 70.5, 68.4, 67.4, 67.1, 62.2, 55.9, 41.4, 30.7, 29.9, 29.6, 26.0, 25.9, 25.4, 19.6 ppm; $[\alpha]_D^{27}$ +6.7° (c = 0.51, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found m/z 751.4073, $C_{46}H_{57}NO_8^+$ requires m/z 751.4084.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[9-(tetrahydropyran-2-yloxy)nonyloxy] piperidine ***(22b)***

Oil, Yield 29%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 7.35-7.23 (20H, m), 5.13 (1H, d, J= 12.4

Hz), 5.08 (1H, d, *J* = 12.4 Hz), 4.68 (1H, d, *J* = 11.5 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.57 (1H, dd, *J* = 2.8, 4.3 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.16-4.04 (2H, m), 3.87 (1H, ddd, *J* = 3.7, 7.0, 10.9 Hz), 3.78-3.61 (7H, m), 3.54-3.30 (4H, m), 1.88-1.41 (10H, m), 1.41-1.20 (10H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 155.7, 138.3, 138.2, 138.0, 136.6, 128.4, 128.3, 127.82, 127.79, 127.7, 127.61, 127.55, 127.50, 127.47, 98.8, 82.3, 78.7, 74.9, 73.02, 72.96, 71.8, 70.6, 68.5, 67.6, 67.1, 62.3, 56.0, 41.5, 30.7, 30.0, 29.7, 29.5, 29.4, 26.2, 26.0, 25.4, 19.6 ppm; $[\alpha]_D^{27}$ +5.6° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 793.4580, $C_{49}H_{63}NO_8^+$ requires *m/z* 793.4554.

(2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[12-(tetrahydropyran-2-yloxy)dodecyloxy] piperidine ***(22c)***

Oil, Yield 25%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 7.35-7.23 (20H, m), 5.13 (1H, d, *J* = 12.4 Hz), 5.08 (1H, d, *J* = 12.4 Hz), 4.69 (1H, d, *J* = 11.6 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 4.57 (1H, dd, *J* = 2.8, 4.1 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.12-4.03 (2H, m), 3.87 (1H, ddd, *J* = 3.9, 7.0, 11.0 Hz), 3.78-3.60 (7H, m), 3.54-3.30 (4H, m), 1.88-1.43 (10H, m), 1.43-1.18 (16H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 155.7, 138.33, 138.28, 138.1, 136.6, 128.4, 128.3, 127.86, 127.83, 127.76, 127.65, 127.58, 127.54, 127.50, 98.8, 82.4, 78.7, 75.0, 73.1, 73.0,

71.8, 70.6, 68.6, 67.7, 67.2, 62.3, 56.1, 41.6, 30.8, 30.1, 29.8, 29.6, 29.5, 26.2, 26.1, 25.5, 19.7 ppm; $[\alpha]_D^{27}$ +10.2° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 835.5048, $C_{52}H_{69}NO_8^+$ requires *m/z* 835.5023.

*4.2.19. Synthesis of (2R,3R,4R,5S)-4,5-dibenzyloxy-1-benzyloxycarbonyl-2-benzyloxymethyl-3-[15-(tetrahydropyran-2-yloxy)pentadecyloxy] piperidine (**22d**)*

Compound **21d** (249.3 mg, 0.569 mmol) and **11** (136.1 mg, 0.24 mmol) was dissolved in THF/DMF (3 mL, 1/1) and NaH (23.2 mg, 0.967 mmol) was added. After stirring for 6 hours, sat. NH_4Cl aq. was added and extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was purified by silica-gel column chromatography (Hexane/EtOAc = 4/1) to give **22d** (80.9 mg, 38%) as an oil. ^1H NMR (270 MHz, CD_3OD, r.t.): 7.33-7.24 (20H, m), 5.13 (1H, d, *J* = 12.4 Hz), 5.08 (1H, d, *J* = 12.4 Hz), 4.69 (1H, d, *J* = 11.5 Hz), 4.64 (1H, d, *J* = 11.8 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 4.57 (1H, dd, *J* = 3.0, 4.1 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.44 (1H, d, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.13-4.04 (2H, m), 3.87 (1H, ddd, *J* = 3.8, 7.1, 11.0 Hz), 3.78-3.62 (7H, m), 3.53-3.30 (4H, m), 1.88-1.43 (10H, m), 1.43-1.21 (22H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 155.7, 138.3, 138.2, 138.0, 136.6, 128.3, 128.2, 127.78, 127.75, 127.68, 127.58, 127.51, 127.46, 127.44, 98.7, 82.3, 78.6, 74.9, 73.0, 72.9, 71.7, 70.5, 68.5, 67.6, 67.1, 62.2, 56.0, 41.5, 30.7, 30.0, 29.7, 29.6, 29.5, 29.4, 26.2, 26.0, 25.4, 19.6 ppm;

$[\alpha]_D^{27}$ +7.7° (*c* = 1.00, $CHCl_3$); HR-FD-MS (positive): $[M]^+$ Found *m/z* 877.5487, $C_{55}H_{75}NO_8^+$ requires *m/z* 877.5493.

4.2.19. General procedure for the synthesis of ***23a-d***

Compound **22** (1 eq.) was dissolved in MeOH/THF (4/1), PPTS (0.5 eq.) was added and stirred for 15 hours at 50 °C. The reaction mixture was acidified by 1 M HCl aq. to pH 2, $Pd(OH)_2$ was added and stirred for 20 hours under hydrogen atmosphere. The mixture was passed through celite pad, evaporated and purified by LiChrolut® RP-18 (Merck Co.) to give **23.**

*(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(6-hydroxyhexyloxy)piperidine hydrochloride (**23a**)*

Crystal, Yield 85%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.92 (1H, td, *J* = 6.3, 9.0 Hz), 3.86 (1H, dd, *J* = 3.3, 11.7 Hz), 3.80 (1H, dd, *J* = 4.4, 11.7 Hz), 3.65 (1H, ddd, *J* = 5.1, 9.0, 11.2 Hz), 3.61 (1H, td, *J* = 6.9, 9.0 Hz), 3.54 (2H, t, *J* = 6.5 Hz), 3.45 (1H, dd, *J* = 9.0, 9.0 Hz), 3.33 (1H, dd, *J* = 9.0, 10.0 Hz), 3.31 (1H, dd, *J* = 5.1, 12.4 Hz), 3.08 (1H, ddd, *J* = 3.3, 4.4, 10.0 Hz), 2.84 (1H, dd, *J* = 11.2, 12.4 Hz), 1.65-1.48 (4H, m), 1.44-1.34 (4H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.4, 77.3, 74.4, 68.8, 62.9, 61.0, 58.7, 47.4, 33.5, 31.2, 27.0, 26.7 ppm; $[\alpha]_D^{27}$ +25.3° (*c* = 1.20, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 264.1829, $C_{12}H_{26}NO_5^+$ requires *m/z* 264.1811.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(9-hydroxynonyloxy)piperidine hydrochloride ***(23b)***

Crystal, Yield 75%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.92 (1H, td, J = 6.3, 8.9 Hz), 3.86 (1H, dd, J = 3.3, 11.7 Hz), 3.81 (1H, dd, J = 4.4, 11.7 Hz), 3.66 (1H, ddd, J = 5.1, 8.9, 11.3 Hz), 3.60 (1H, td, J = 6.6, 9.0 Hz), 3.53 (2H, t, J = 6.5 Hz), 3.45 (1H, dd, J = 8.9, 8.9 Hz), 3.33 (1H, dd, J = 8.9, 10.0 Hz), 3.30 (1H, dd, J = 5.1, 12.4 Hz), 3.08 (1H, ddd, J = 3.3, 4.4, 10.0 Hz), 2.84 (1H, dd, J = 11.3, 12.4 Hz), 1.64-1.46 (4H, m), 1.42-1.28 (10H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.4, 33.6, 31.3, 30.7, 30.5, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +19.7° (c = 0.60, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found m/z 306.2252, $C_{15}H_{32}NO_5^+$ requires m/z 306.2280.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(12-hydroxydodecyloxy)piperidine hydrochloride ***(23c)***

Crystal, Yield 81%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.92 (1H, td, J = 6.5, 8.9 Hz), 3.85 (1H, dd, J = 3.3, 11.7 Hz), 3.80 (1H, dd, J = 4.3, 11.7 Hz), 3.65 (1H, ddd, J = 5.0, 8.9, 11.3 Hz), 3.60 (1H, td, J = 6.6, 8.9 Hz), 3.53 (2H, t, J = 6.5 Hz), 3.45 (1H, dd, J = 8.9, 8.9 Hz), 3.33 (1H, dd, J = 8.9, 10.2 Hz), 3.30 (1H, dd, J = 5.0, 12.4 Hz), 3.08 (1H, ddd, J = 3.3, 4.3, 10.2 Hz), 2.84 (1H, dd, J = 11.3, 12.4 Hz), 1.62-1.46 (4H, m), 1.42-1.28 (16H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.3, 33.7, 31.3,

30.7, 30.6, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +20.4° (*c* = 0.39, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 348.2726, $C_{18}H_{38}NO_5^+$ requires *m/z* 348.2750.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(15-hydroxypentadecyloxy)piperidine hydrochloride ***(23d)***

Crystal, Yield 48%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.92 (1H, td, *J* = 6.4, 8.9 Hz), 3.85 (1H, dd, *J* = 3.3, 11.7 Hz), 3.80 (1H, dd, *J* = 4.2, 11.7 Hz), 3.63 (1H, ddd, *J* = 5.1, 8.9, 11.3 Hz), 3.59 (1H, td, *J* = 6.5, 9.0 Hz), 3.52 (2H, t, *J* = 6.5 Hz), 3.44 (1H, dd, *J* = 8.9, 8.9 Hz), 3.32 (1H, dd, *J* = 8.9, 10.2 Hz), 3.30 (1H, dd, *J* = 5.1, 12.2 Hz), 3.07 (1H, ddd, *J* = 3.3, 4.4, 10.2 Hz), 2.83 (1H, dd, *J* = 11.3, 12.2 Hz), 1.63-1.46 (4H, m), 1.40-1.27 (22H, m) ppm, ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.5, 77.3, 74.6, 68.8, 63.0, 61.0, 58.7, 47.3, 33.6, 31.3, 30.8, 30.8, 30.7, 30.61, 30.59, 27.2, 26.9 ppm; $[\alpha]_D^{27}$ +22.6° (*c* = 0.67, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 390.3199, $C_{21}H_{44}NO_5^+$ requires *m/z* 390.3219.

4.2.20. Synthesis of ***23e,f***

Protective groups of **19e** and **19f** were removed by the method written in §4.2.9 to give **23e,f**.

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(4-hydroxybutyloxy)piperidine hydrochloride ***(23e)***

Crystal, Yield 93%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.98-3.91 (1H, m), 3.83 (2H, d, *J* =

3.9 Hz), 3.69-3.60 (2H, m), 3.57 (1H, t, *J* = 6.1 Hz), 3.46 (1H, dd, *J* = 8.9, 8.9 Hz), 3.34 (1H, dd, *J* = 8.9, 10.2 Hz), 3.30 (1H, dd, *J* = 4.9, 12.2 Hz), 3.08 (1H, dt, *J* = 10.2, 3.9 Hz), 2.84 (1H, dd, *J* = 11.4, 12.2 Hz) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.5, 77.3, 74.3, 68.8, 62.7, 61.0, 58.7, 47.3, 30.2, 27.7 ppm; $[\alpha]_D^{27}$ +28.1° (*c* = 0.25, MeOH); HR-FAB-MS (positive): $[M+H]^+$ Found *m/z* 236.1515, $C_{10}H_{22}NO_5^+$ requires *m/z* 236.1498

(2R,3R,4R,5S)-4,5-dihydroxy-2-hydroxymethyl-3-(5-hydroxypentyloxy)piperidine hydrochloride ***(23f)***

Crystal, Yield 93%; ^{1}H NMR (270 MHz, CD_3OD, r.t.): 3.93 (1H, td, *J* = 6.4, 9.0 Hz), 3.87 (1H, dd, *J* = 3.0, 12.0 Hz), 3.82 (1H, dd, *J* = 4.2, 12.0 Hz), 3.66 (1H, ddd, *J* = 5.1, 8.9, 11.1 Hz), 3.65-3.58 (1H, m), 3.55 (2H, t, *J* = 6.3 Hz), 3.46 (1H, dd, *J* = 8.9, 8.9 Hz), 3.34 (1H, dd, *J* = 8.9, 10.1 Hz), 3.30 (1H, dd, *J* = 5.1, 12.4 Hz), 3.09 (1H, ddd, *J* = 3.0, 4.2, 10.1 Hz), 2.84 (1H, dd, *J* = 11.1, 12.4 Hz), 1.67-1.39 (6H, m) ppm; ^{13}C NMR (67.5 MHz, CD_3OD, r.t.): 78.4, 77.3, 74.4, 68.8, 62.8, 61.0, 58.7, 47.3, 33.4, 31.0, 23.5 ppm; $[\alpha]_D^{27}$ +26.0° (*c* = 0.58, MeOH); HR-FD-MS (positive): $[M]^+$ Found *m/z* 249.1594, $C_{11}H_{23}NO_5^+$ requires *m/z* 249.1576.

4.3. Assay procedure of α-amylase inhibitory activity

Samples dissolved in 20% DMSO aq. (10 μL), porcine pancreatic α-amylase (1 unit/mL, 10 μL) and buffer solution (100 mM Sodium phosphate, 50 mM sodium chloride, pH 6.9,

30 μL) were mixed and pre-incubated at 37 ºC for 5 min. To this mixture, 2,4-dinitrophenyl maltotriose (2 mM, 50 μL) dissolved in the buffer solution was added to start the enzyme reaction. Absorbance at 405 nm was monitored temporally to determine the rate of enzyme reaction. Inhibition rate was determined by comparing the rate of hydrolysis between control reaction (without sample) and sample reaction. Each experiment was repeated at least 3 times to determine IC_{50} value or inhibition%.

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